Non-Invasive Pulsatile Shear Stress Modifies Endothelial Activation

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The luminal surface of all the vasculature and the heart is lined by endothelial cells (EC), encompassing more than 5000 m^2. Furthermore, the response of EC to external signals and the synthesis and production of various mediators is heterogeneous and adaptive based on location and signals. EC membranes are the sensing mechanism, responsive to mechanical (shear stress) and biochemical signaling (chemosensor). EC output is important for blood fluidity, coagulation, vasoreactivity, vasculogenesis, barrier function, and inflammation. Endothelial cell activation is the process by which EC changes from a quiescent cell phenotype, which maintains cellular integrity, antithrombotic, and anti-inflammatory properties, to a prothrombotic, pro-inflammatory, and permeable phenotype, also at the site of injury or infection, involved in repair and leukocyte trafficking. Endothelial activation is triggered by a multitude of stimuli that include inflammatory cytokines (interleukins, tumor necrosis factor, and interferon-γ), bacterial endotoxins, and pattern recognition receptor activation (PRR) after recognition of pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMP). Pathological activation of EC leads to increased vascular permeability, thrombosis, and an uncontrolled inflammatory response leading to endothelial dysfunction; the latter can be contained at the local level or participate in a more profound systemic response leading to multiorgan dysfunction and death.

Keywords: pulsatile shear stress ; whole body periodic acceleration ; exercise ; enhanced external counterpulsation ; whole body vibration

1. Models of Endothelial Activation

1.1. Ischemia Reperfusion Injury (IRI)-Cardiac Arrest (CA) and Myocardial Infarction (MI)

Estimates indicate that in the United States there are more than 500,000 cases annually of outpatient and in-hospital cardiac arrest, with a return to spontaneous circulation (ROSC) of 40–50% and a survival rate to hospital discharge of 10.5% and 26.7% for outpatient and in-hospital cardiac arrest, respectively [1]. Postcardiac arrest syndrome (PCAS) is characterized by reperfusion injury from systemic ischemia, myocardial dysfunction, brain, and other vital organ injury, superimposed on underlying diseases, all of which explain the low survival rate of hospital discharge. After CA, a systemic inflammatory response occurs that has been shown to occur in the reperfusion stage, with the release of pro-inflammatory cytokines by leukocytes and endothelial cells through the activation of leukocytes and endothelial cells and the release of secondary cytokines [2][3][4][5][6][7][8][9]. EC expresses a wide spectrum of cytokines and chemokines, including pro-inflammatory interleukins; IL-1β, IL-3, IL-5, IL-6, IL-8, IL-11, IL-15, and tumor necrosis factor (TNF-α), as well as anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra), IL-10, IL-13, and transforming growth factor beta (TGF-β) [10][11][12].

Recent data in mice show that myocardial infarction (MI) produces remote global endothelium activation, with up-regulation of the vascular cell adhesion molecule (VCAM-1), the cell adhesion molecule (P-Selectin) and platelet adhesion in remote arterial and microvascular beds, which persists for longer periods in animals with preexisting atherosclerosis [13][14]. Several reviews have outlined the role of NO in the cardiovascular system [15][16]. CA and resuscitation are models of total-body IRI, while MI with and without reperfusion are models of focal injury. These two models offer the opportunity to study what has been termed “sterile” endothelial activation [17].

1.2. Sepsis and Lipopolysaccharide-Induced Sepsis Syndrome (LPS)

In 2017, the estimated global burden of sepsis was 48.9 million people worldwide, with a mortality of 11 million. In the United States, for example, sepsis is the most common cause of in-hospital deaths and costs more than USD 2 billion annually [18]. Sepsis is a dysregulated response to infection that triggers a complex set of pathways and a cellular response that includes endothelial activation, macro, and micro circulatory failure, ultimately leading to organ failure and

death. The systemic response may be triggered by the recognition of a pathogen (Pathogen Associated molecular pattern, PAMP) and or cellular injury proteins (damage associated molecular pattern, DAMP) recognition. The initial response predominantly by immune cells is the release of cytokines, interleukins, chemokines, interferons, tumor necrosis factor (TNF-α), and growth factors. The initiation of the inflammatory cascade is orchestrated by nuclear factor kappa beta (NFƙ-β). The target of cytokines is the EC; however, these are also capable of secreting cytokines. During sepsis, the role of EC is to amplify the immune response and activate the coagulation system, with endothelial activation ultimately contributing to end organ damage and microcirculatory failure [17][19][20]. In endotoxin (Escherichia Coli) -induced lipopolysaccharide sepsis-like syndrome (LPS), bacterial cell wall products ultimately bind to the toll-like receptor-4 (TLR-4) on the endothelial cell wall, to induce the intracellular response of EC of cytokines, adhesion molecules, and reactive oxygen species (ROS), and similarly amplify the immune response. Elevated biomarkers of endothelial activation/dysfunction in the systemic inflammatory response of critical illnesses and sepsis have been shown to be associated with a higher risk of developing respiratory failure, multiple-organ dysfunction, and death [21][22][23][24]. The decrease in NO bioavailability also plays a role in sepsis. Systemic NO release during sepsis has been shown and later thought to be responsible for hemodynamic and vascular instability, prompting the use of a non-selective inhibitor of NO (L-NAME) as a clinical therapeutic intervention in sepsis, which failed [25][26]. In animal models, an increase in NO bioavailability using NO donors or arginine administration, or a decrease in asymmetric dimethylarginine (ADMA, an endogenous inhibitor of nitric oxide synthase) appears to show some promise [27]. It is important to note that the reduced bioavailability of NO at the microvascular level comes primarily from the reduction in eNOS produced by the EC and that produces small amounts of NO, in contrast to iNOS which produces large amounts of NO, primarily by neutrophils and macrophages. NO derived from eNOS has been shown to be protective in sepsis [28][29]. Thus, increasing the bioavailability of NO through eNOS would provide a new avenue of therapeutics [16][30][31].

2. Exercise

2.1. Exercise for Pulsatile Shear Stress

Exercise is defined as “a subset of physical activity that is planned, structured, and repetitive and has as a final or intermediate objective the improvement or maintenance of physical fitness” [32][33]. Herein, the exercise strategies considered involve walking, jogging, or running. PSS and/or circumferential wall stress or stretch (which arises from the effect of blood pressure on the vascular wall and is applied to all layers of the arterial wall) are the primary signals produced by EXER that are mechanically transduced by the EC [34][35][36][37][38][39][40][41][42].

During walking, jogging, or running, pulses are added to the circulation as a result of the frequency of cadence of the foot. The frequency of steps for both men and women who are recreational runners has been estimated to be between 163 and 169 steps per min [43]. This frequency, added to a baseline pulsatility of 60–100 beats/min, generates total pulsation close to 220–240 beats per min (3–4 Hz) during running. Since running is not timed for the cardiac cycle, the expected pulsatility frequencies are in the range of 1.3 to 4 Hz.

Herein, it will not discuss the various exercise strategies or mechanisms of exercise-induced cardioprotection that others have thoroughly reviewed [44][45][46][47][48][49][50][51][52][53][54]. Exercise reduces cardiovascular morbidity and mortality and is positively correlated with beneficial health outcomes but requires subject cooperation and thus may prevent patients from participating and remaining in an exercise program, particularly those in an intensive care setting or those with physical and cognitive limitations.

2.2. Exercise (EXER) and Ischemia Reperfusion Injury

Exercise is a well-known cardioprotective strategy. Physical activity, exercise, and a healthy diet are the pillars of cardiovascular health [55]. Exercise induces a variety of cardioprotective signals, including a decrease in the inflammatory phenotype [54]. Regular exercise induces interleukin-6 (IL-6) produced by muscle fibers, which stimulates anti-inflammatory cytokines (IL-1ra and IL-10) and inhibits tumor necrosis alpha (TNF-α) [56]. In a recent systematic review and meta-analysis, regular exercise decreased aging-induced inflammasome activation related to inflammatory cytokines (IL-1β and IL-18) [57]. In exercised (voluntary free-wheel running) mice fed a high-fat diet, exercise suppressed the pyrin domain of the NOD-like receptor family containing the 3 (NLRP3) inflammasome, improved nitric oxide production, and reduced oxidative stress [58].

Two specific periods have been explored concerning the role of EXER in cardiovascular protection against IRI or MI: EXER as a preconditioning (pretreatment) strategy (EXER performed prior to the onset of IRI) and a postcondition (post-treatment) strategy (EXER, performed after IRI). Both strategies aim to induce cardioprotection through various pathways, which ultimately increase myocardial tolerance, reduce the size of the infarct, and IRI-induced arrythmias. The effects of

exercise preconditioning against IRI have been well-established in animal models and human epidemiological studies summarized by Borges et al. [59]. Additionally, the beneficial effects of exercise after MI have also been well established, with exercise being an important component of the post-MI rehabilitation program [60]. However, a link between cardioprotection induced by exercise and decreased endothelial activation remains to be established. Exercise has been shown to increase the bioavailability of NO, specifically eNO and IL-6, both of which play an anti-inflammatory role [61][62][63]. It is important to note that excessive, prolonged, and strenuous overtraining can lead to damaging oxidative stress, with an attendant decrease in NO bioavailability. The concept of redox and exercise-induced hormesis has been advanced and previously reviewed; therefore, it appears that too much of a good thing may not necessarily be effective when it comes to EXER [33][64][65][66][67][68].

Data on the beneficial effects of EXER as a pre- or post-conditioning strategy for cardiac arrest and resuscitation are scarce. There is little doubt about the cardioprotective role of EXER and physical activity, on overall cardiovascular health suggesting a beneficial effect of EXER, and the benefits of post-MI EXER rehabilitation [69][70][71]. Recent data from the Korean National Outpatient CA registry showed that patients with higher intensity physical activity during exercise before and index CA had better survival outcomes and a successful percutaneous coronary intervention [72] suggesting a protective role for EXER specifically in CA.

2.3. Exercise and Sepsis

The effects of exercise on survival in animal models of sepsis and LPS have been well-documented, showing a favorable survival response to various EXER interventions [73][74][75][76][77][78][79][80].

Gholamnezhad et al. recently performed a systematic review of the modulatory effects of EXER on LPS-induced lung inflammation. The results showed that aerobic exercise (prior to LPS) in rodents reduced LPS-induced oxidative stress, inflammation, protein leakage, levels of IL-6, IL-1β, IL-17, TNF-α, granulocyte–macrophage colony stimulating factor, and improved IL-10 and IL-1Ra, and a change in the balance between pro-inflammatory and anti-inflammatory phenotype, thus supporting the role of exercise in LPS-induced lung injury [81].

In human studies, the effects of exercise on sepsis have also been reported in a limited number of studies. Low rates of physical exercise and high rates of watching television (physical inactivity) are associated with higher morbidity and mortality from community-acquired sepsis [65], and physical rehabilitation in septic patients was shown to improve physical function and reduce the inflammatory response [82][83]. A review on the effects of exercise in the treatment of sepsis in animal models and patients has recently been published [84].

3. Enhanced External Counterpulsation

3.1. Enhance External Counterpulsation (EECP) for Pulsatile Shear Stress

Enhanced external counterpulsation (EECP) involves compression of the legs to buttocks using pneumatic cuffs, timed to early diastole [85][86]. EECP induces pulsations and imparts a circumferential stretch that doubles the heart rate (2–3.3 Hz). The beneficial clinical effects of EECP have been reported for angina, peripheral artery disease, diabetes, erectile dysfunction, and possibly Alzheimer’s disease. Similarly, to exercise, EECP via PSS induces NO production [87], improves endothelial function [88][89], and attenuates pro-inflammatory signaling pathways [90][91]. The risks and guidelines of EECP have been published by Lin et al. [92].

3.2. Enhanced External Counterpulsation (EECP) and Ischemia Reperfusion Injury

The use of EECP on acute and chronic MI-induced IRI has been shown in both animal models and human studies and has been reviewed [85], and its use as a myocardial conditioning strategy has also been reviewed [93].

In nonischemic hypercholesterolemic patients, seven weeks of EECP was compared with the control. The EECP group had a significant reduction in atherosclerosis lesion, and a reduction in C-reactive protein, vascular cell adhesion molecule-1(VCAM-1), iNOS, mitogen-activated protein kinase phosphorylation (MAPK-p38), and activation of NFƙ-β [90].

In a dog model of MI by coronary artery occlusion, EECP use significantly improved myocardial perfusion and function after 4 and 6 weeks of EECP compared to controls, along with increased expression of vascular endothelial growth factor (VEGF) and increased microvascular density [94]. EECP has also been studied in a dog model of CA. Post-CA EECP (4 h of use after CA) increased cerebral blood flow, improved microcirculation recovery, and improved neurological outcomes

from 24 to 96 h compared to control animals [95]. In a similar dog model of CA with also 4 h of EECP post-CA, others have also shown improved survival and myocardial function [96].

Casey et al. and Braith et al. studied the effects of EECP in patients with chronic angina and symptomatic coronary artery disease, respectively. Both investigators showed a significant reduction in TNF-α, monocyte chemoattractant protein-1 (MCP-1), and soluble vascular adhesion molecule (sVCAM-1) compared to controls [89][97]. Yang et al. have summarized the additional benefits of EECP beyond hemodynamics [98].

3.3. Enhanced External Counter Pulsation and Sepsis

The effects of EECP on sepsis or LPS animal models have not been published. A single case study has documented the use of EECP in a female patient diagnosed with coronavirus disease 2019 (COVID-19) and treated at home with a cocktail of vitamins and hydroxychloroquine for 6 days. Most of her symptoms resolved but remained with fatigue, headaches, and shortness of breath at rest and during activities, and “brain fog” (subjective lack of clarity) for months. She was treated with 35 sessions of EECP, and the aforementioned symptoms resolved. The resolution of symptoms was subjectively measured, and this resolution was attributed to the use of EECP [99].

4. Whole-Body Vibration

4.1. Whole-Body Vibration (WBV) for Pulsatile Shear Stress

The effects of vibration on the entire body were first described in the 1900s and began to appear in the scientific literature in the 1960s describing the effects of whole-body vibration (WBV) on ventilation, behaviors, and central hemodynamics [100][101][102][103].

The mechanical oscillations imparted by WBV are performed using a platform, moving in a linear or pivotal motion with a standing or seated subject at frequencies from 12–60 Hz and displacements from 1 to 10 mm producing accelerations of + 1.5 mt/sec^2 [104][105][106][107][108]. Most studies exploring the effects of WBV use a structured exercise program performed on the WBV platform. WBV has been shown to increase skin blood flow [109][110][111], improve endothelial function in an elderly population [112], and its effect is summarized by others [113][114][115].

4.2. Whole-Body Vibration and Ischemia Reperfusion Injury

WBV has been used as a pretreatment strategy in a rodent model of acute MI without reperfusion. WBV was carried out for 1 and 3 weeks (30 min per day for 6 days) versus a control group. Myocardial infarct size and severity of ventricular fibrillation were significantly lower in WBV at 1 and 3 weeks [116]. WBV has also been used as an adjunct to a cardiac rehabilitation program over a 24-days, both standard exercise rehabilitation and those who received adjunct WVB had improvement in exercise tolerance and left ventricular ejection fraction, and both groups obtained similar effects [117]. There are no published results on the use of WBV post CA, likely due to the need for subject cooperation and the critical nature of these patients.

4.3. Whole-Body Vibration and Sepsis

Similarly, to EXER, data on WBV applied in the setting of sepsis or LPS are scarce. A single study explored the effects of WBV on LPS-induced inflammatory bone loss. The report focused on trabecular bone loss, which decreased with WBV. Furthermore, in the same study using in vitro stimulation of human mesenchymal stromal cells with WBV, WBV reduced the increase in LPS-induced IL-1β and TNF-α induced by LPS [118]. Two recent reviews have addressed the potential for WBV to improve acute and long-term clinical conditions associated with COVID-19 and provide a framework for the use of WBV in the acute care setting [119][120].

Sanni et al. investigated the acute effects of WBV (HI = 88.7 ms^2 and LO =44.4 ms^2, both at 30 Hz) in healthy volunteers. They report a higher muscle oxygen consumption in the LO compared to the HI group and an increase in IL-6 in both groups but a higher in the LO [121]. Rodriguez-Miguelez studied healthy elderly volunteers (70 years) who performed an 8-week training protocol on WBV. WBV produced a significant decrease in TNF-α, and an increase in IL-10, and a significant decrease in the mediator myeloid differentiation response gene88 (MyDD88, an essential protein in the production of inflammatory cytokines) and transcription factor p65 (also known as the nuclear factor NF-β p65 subunit) [122]. In contrast, Jawed et al. showed in healthy male volunteers trained on WVB (35 Hz, eight 60 s sets, with 2 min between sets) an increase in IL-10 and an increase in TNF-α [123]. Similarly, Neves et al., in adult patients with chronic obstructive pulmonary disease (45–80 years) enrolled in a 12-week WBV protocol, and Cristi et al., in a 9-week WBV protocol in elderly volunteers (80 years), failed to show changes in IL-6 or soluble receptors of TNF, TNF-α, IL-10, and IL-

1β [124][125]. Therefore, the effects of WBV on the parameters of inflammation and endothelial activation markers remain inconsistent.

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