Mechanistic Effects of Exercise Training in Preventing or Attenuating Atherosclerosis

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INTRODUCTION

Exercise training alone or as core component of cardiac rehabilitation (CR) programs is endowed with a wide array of beneficial effects including mortality reduction (91), prevention of cardiac remodelling (41,44), and improvement of cardiovascular functional capacity and myocardial perfusion (36,37,45,48) in patients with coronary artery disease (CAD). The improvement of endothelial function (113), the anti-inflammatory properties (18,38), the improvement of neurohormonal and autonomic balance (42,43,46,47,108), and the reduction of oxidative stress (92) might represent some of the putative mechanisms by which exercise training exerts its beneficial effects. However, the physiological underpinnings of the positive impact of exercise training are not fully understood.

CAD remains the main cause of mortality in developed countries (33,125). In the last decades the understanding of the pathogenesis of atherosclerosis has dramatically changed. Atherosclerosis is considered a dynamic and gradual process of chronic low-grade inflammation and endothelial dysfunction involving the cellular infiltration of several cell types, including monocytes and T lymphocytes (61). Monocytes interact with the endothelial layer, attach firmly to the endothelium, and then migrate into the subendothelial space to differentiate into macrophages. Macrophages release cytokines and can also become foam cells by taking up lipids. Macrophages and foam cells secrete growth factors; this leads to cell proliferation and matrix production. Thus, macrophages and foam cells both contribute to lesion growth and may contribute to instability and thrombotic events (77,94).

This paper reviews the effects of exercise training on markers of inflammation, cellular adhesion molecules, endothelial progenitor cells, microRNAs, endothelial function, and oxidative stress in patients with CAD.

EFFECTS OF EXERCISE TRAINING ON CYTOKINES

The pathogenesis of atherosclerosis involves several cytokines belonging to the interleukin group (i.e., IL-1, IL-6, IL-8, IL-10) and macrophage associated cytokines such as tumor necrosis factor-α (TNF-α), interferon (IFN)-γ and colony stimulating factors (68). Cytokines can be categorized as pro-inflammatory (pro-atherogenic) and anti-inflammatory (anti-atherogenic). Both pro-inflammatory and anti-inflammatory cytokines play a key role in chronic vascular inflammation, and their balance seems paramount to the progression of atherosclerotic disease (68). In brief, the pro-inflammatory cytokines exert several biological functions, including: (a) the induction of other proinflammatory cytokines and chemokines; (b) the expression of adhesion molecules on endothelial cells; (c) the stimulation of cell proliferation and differentiation; (d) the release of matrix-degrading enzymes; and (e) the regulation of acute-phase reaction. On the other hand, anti-inflammatory cytokines exhibit atheroprotective properties, inhibiting a wide range of immune and inflammatory responses, including the inhibition of pro-inflammatory cytokines.

The anti-inflammatory effect of exercise in patients with CAD has been assessed through the measurement of circulating levels of the pro-inflammatory cytokines IL-1, IL-6, IL-8, TNF-α, and IFN-γ, and of the anti-inflammatory cytokine IL-10 (53,67,84,87,106,121). There is moderate evidence that exercise training reduces the levels of IL-6 (16,53,103,105,117). These studies indicate that exercise training reduces vascular wall inflammation, by increasing the levels of IL-10 (53,106,109) and reducing the levels of some pro-inflammatory cytokines (53,67,121,84,109) (Table 1).

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TABLE 1. The effect of exercise training on inflammatory biomarkers of atherosclerosis among patients with coronary artery disease.

First Author, Year (reference)	n	RCT	Follow-Up	Intervention	CRP	TNF-α	IFN-γ	IL-6
Smith et al., 1999 (109)	43	No	6 mo	Aerobic and resistance exercise training: subjects averaged 70 min per session, 2 d·wk^{-1}	↔	↓	↓	
Milani et al., 2004 (81)	277	No	12 wk	Aerobic exercise training: 3 d·wk^{-1}	↓			
Goldhammer et al., 2005 (52)	28	No	12 wk	Aerobic exercise training: 45 min; 3 d·wk^{-1}	↓			
Caulin-Glaser et al., 2005 (14)	172	No	12 wk	Aerobic exercise training: 3 d·wk^{-1}	↓			
Cesari et al., 2009 (16)	86	No	2 wk	Aerobic exercise training: 6 d·wk^{-1}				↓
Huffman et al., 2006 (63)	193	Yes	6 mo	Aerobic exercise training: three exercise groups based on exercise volume and intensity	↔			
Lavie et al., 2006 (73)	365	No	12 wk	Aerobic exercise training: 30 to 40 min, 3 d·wk^{-1}	↓			
Niessner et al., 2006 (84)	32	No	3 mo	Aerobic exercise training: ≥30 min, ≥3 d·wk^{-1}	↔			↔
Schumacher et al., 2006 (105)	197	Yes	6 mo	Lifestyle intervention with aerobic exercise training: 45 min of supervised exercise, 2 d·wk^{-1} for 15 wk, plus home-based exercise		↓[a]		↓[a]
Shin et al., 2006 (106)	39	No	14 wk	Three study groups (exercise, exercise + statins, statins only) Aerobic exercise training: 30 to 40 min, 3 d·wk^{-1}	↓[b]			
Goldhammer et al., 2007 (53)	28	No	3 mo	Aerobic exercise training: 45 min, 3 d·wk^{-1}	↓		↓	↓
Kim et al., 2008 (67)	39	No	14 wk	Aerobic exercise training: 30 to 40 min, 3 d·wk^{-1}	↓	↓		↓
Pluss et al., 2008 (90)	224	Yes	12 wk	Two study groups (standard and expanded exercise program) Aerobic exercise training: 60 min, 2 d·wk^{-1}	↓[c]			
Walther et al., 2008 (121)	66	Yes	24 mo	Aerobic exercise training: 20 to 60 min, 7 d·wk^{-1}	↓			↓
Lara-Fernandez et al., 2011 (71)	34	Yes	16 wk	Aerobic (40 min) and resistance (10 min) exercise training: 3 d·wk^{-1}	↓			

CRP = high sensitivity C-reactive protein; IFN-γ = interferon-γ; IL-6 = Interleukin-6; RCT = randomized controlled trial; TNF-α = tumor necrosis factor-α.
[a]decrease was also observed in the control group
[b]significant for exercise plus statin group only
[c]significant for both groups

EFFECTS OF EXERCISE TRAINING ON C-REACTIVE PROTEIN

C-reactive protein (CRP) is an acute phase protein largely produced by the liver in response to inflammatory cytokines, primarily IL-6, and, to a lesser extent, IL-1 and TNF-α (13). CRP is an important marker of subclinical chronic vascular inflammation, being considered a strong predictor of cardiovascular events (115). CRP is a pro-inflammatory mediator that contributes to the development and progression of atherosclerosis through: (a) the increase of low-density lipoprotein (LDL) uptake by macrophages (128); (b) the mediation of intercellular adhesion molecule-1 (ICAM-1) and soluble vascular cell adhesion molecule-1 (VCAM-1) expression and the mediation of monocyte chemotactic protein-1 induction (88,89); (c) the induction of tissue factor production by monocytes (15); (d) the induction of plasminogen activator inhibitor-1 (PAI-1) expression (28); and (e) the decrease of the production of nitric oxide (NO) by endothelial cells (118).

Previous studies investigated the effects of exercise training on CRP and found a significant reduction in levels after a 3 mo intervention in patients with CAD with and without metabolic syndrome, independent of weight and statin therapy (14,80,81). Moreover, an exercise-induced reduction of CRP levels independent of weight-loss and

statins has been reported (53,90,121). Walther et al. (121) randomized 101 patients with stable CAD to either percutaneous intervention with stent or aerobic exercise training. In a subgroup of 66 patients, after 24 mo of training, CRP levels were reduced by 41%, whereas no change was observed in the percutaneous intervention group. Of note, the effects of exercise were independent of statin therapy.

A number of studies have examined the anti-inflammatory potential of exercise in patients with CAD through the assessment of circulating CRP levels (Table 1). Taken together, data from these studies indicate that exercise training reduces the circulating levels of CRP. Several prospective studies examining the influence of exercise training alone or incorporated in multi-disciplinary cardiac rehabilitation programs (exercise training program, dietary and lifestyle counseling, psychological support) on markers of inflammation, have suggested an anti-inflammatory effect of chronic exercise (6,14,16,33,46,52,53,60–63,67,68,71,73,76,77,80,84,86,87,90,92–94,101,103,105,107–109,117,121,125) (Table 1). As pointed out in Table 1, the majority of evidence suggests that exercise training is related to improvement in low-grade inflammatory markers as expressed by circulating CRP levels. However, in their systematic review, Kasapis et al. (65) reported conflicting results between studies. This discrepancy may be due to differences in subject characteristics and sample size, to the timing of the blood samples taken, and the type, intensity, and duration of the exercise intervention. The duration of the exercise interventions seems to be crucial, since the majority of studies show improvements in inflammatory markers with at least 12 wk of exercise intervention. Several potential mechanisms are putatively involved in decreasing CRP induced by exercise training alone or as a core component of a multi-disciplinary cardiac rehabilitation program; all of them are closely related to the decrease of cytokine production, namely IL-6, IL-1, and TNF-α (74).

The improvement of central obesity, with a consequent decrease in the adipocytes production of inflammatory cytokines, is one of the main determinants. It is well documented that central obesity is associated with increased CRP levels (78,61), possibly due to increased adipocyte-induced production of the inflammatory cytokines IL-6 and TNF-α (49). Accordingly, exercise could mitigate inflammation by reducing body weight. However, it has been reported that exercise training reduces the circulating levels of IL-6, IL-1, and CRP levels independent of changes in body mass (53,121), suggesting that other factors may contribute to the exercise-related anti-inflammatory effect. The decreased production of cytokines in others sites beyond adipose tissue, such as skeletal muscle and mononuclear cells could be pointed out as another possible mechanism mediating the anti-inflammatory effect of exercise. In patients with heart failure, 6 mo of exercise training reduced the skeletal muscle TNF-α, IL-1β, and IL-6 expression. However, the serum levels of the previously mentioned parameters remained unaffected, raising the question of whether this local change bears systemic pathophysiological reverberations (56).

EFFECTS OF EXERCISE TRAINING ON ENDOTHELIAL FUNCTION

The integrity of the endothelium is crucial for preserving vascular homeostasis (1,11). Endothelial function has extensively been assessed as endothelium-dependent vasomotion, at least in part based on the assumption that impaired endothelium-dependent vasodilation also reflects the alteration of other important functions of the endothelium (27). Endothelial dysfunction can be defined as an alteration in the basal endothelial phenotype (vasorelaxant, anticoagulant, antiplatelet, and profibrinolytic), to one that is vasoconstrictive, procoagulant, platelet-activating, and antifibrinolytic (3). The dysfunctional endothelial cells release lower levels of nitric oxide (NO), prostacyclin, thrombomodulin, and tissue plasminogen activator and meanwhile increase levels of endothelin-1, angiotensin II, PAI-1, and von Willebrand factor (3). Tissue factor X, which is not present on the functional endothelial cell surface, becomes expressed as a result of thrombin production. Thrombin is activated through the binding of activated factor V to activated factor X on the surface of the endothelial cell (3).

NO is generated by the oxidation of L-arginine into L-citruline by the action of nitric oxide synthase (NOS). NO plays a pivotal role in the regulation of vascular tone, the inhibition of platelet aggregation, and the control of the cytokine adhesion to the vessel wall (20). In atherosclerotic vessels, the reduction of NO bioavailability is associated with vasoconstriction, platelet adherence and aggregation, leukocyte adherence to the endothelium, and increased proliferation of vascular smooth muscle cells (96). The degradation of NO through the interaction with reactive oxygen species (ROS) is considered the main pathway responsible for the decrease of NO bioavailability (57). In addition, atherosclerosis also promotes the downregulation of endothelial NOS (eNOS) with a consequent decrease in the production of NO.

Several studies explored NO bioavailability indirectly by measuring the degree of endothelium-dependent vasodilatation (51,59). Those studies consistently showed that exercise training, particularly aerobic exercise, promotes favorable adaptations in endothelial cell function with evident clinical benefits. Therefore, regular exercise is viewed as a non-pharmacological therapeutic modality that enhances endothelial function in patients with established CAD (58) and heart failure (9). In brief, the exercise-induced increase of NO bioavailability could be the result of the increased activity/expression of eNOS, and/or the diminished degradation of NO as a result of the reduced interaction with ROS.

Hambrecht et al. (59) demonstrated the positive effects of exercise training on vascular function and eNOS expression in the human vascular system, showing a 2-fold increase in eNOS mRNA expression and a 3.2-fold increase in the phosphorylation of eNOS on serine 1177 residue after 4 wk of regular exercise training in patients with CAD (59). These changes led to a rise in the enzymatic activity of eNOS and consequently to an enhanced NO production (59). Furthermore, regular exercise tends to increase antioxidant defenses

by enhancing the activity of superoxide dismutase and glutathione peroxidase and as a result reducing NO degradation (55). The increase of antioxidant defenses could also contribute to attenuating the formation of foam cells and vascular inflammation through the reduction of LDL oxidation (55). In fact, lipid oxidation as the result of LDL exposure to the oxidative waste of intima layer seems to be essential for the foam cells formation, as native LDL is rapidly taken up by macrophages.

In summary, regular exercise promotes the acute increase of blood flow and shear stress and, in turn, improves the NO bioavailability, hence increasing endothelium-dependent vasodilatation. This improvement may represent the principal pathophysiological mechanism underpinning the observed reduction of myocardial ischemia through regular exercise (51,59). Interestingly, it should be noted that exercise intensity seems to be a crucial variable in this vascular response. In fact, moderate-intensity aerobic exercise increases endothelium-dependent vasodilatation in subjects with impaired endothelial function (55). Nevertheless, recent evidence in patients with chronic heart failure suggests that high-intensity aerobic interval exercise may be better than moderate-intensity aerobic exercise to increase endothelial function and NO availability (124).

EFFECTS OF EXERCISE TRAINING ON CELLULAR ADHESION MOLECULES

Under physiologic conditions, the endothelial cell does not express molecules that induce the adhesion of circulating leukocytes. However, the activation of the endothelial cell by cytokines, oxidized LDL, and ROS induce the endothelial expression of cellular adhesion molecules—such as ICAM-1, VCAM-1, E-selectin, and P-selectin—that are crucial to the recruitment of inflammatory cells to the vessel wall (35). These molecules can be measured in the circulation as soluble adhesion molecules since they are released in soluble form into the bloodstream from the proteolytic cleavage of membrane-bound molecules. Therefore, these molecules are considered to be important markers of endothelial cell activation and inflammation (35). Several studies explored the effect of exercise training on adhesion molecules (1,62,71,86,93,98,101,105). Exercise training exerts a positive impact on circulating cellular adhesion molecules (Table 2). There is moderate evidence that aerobic exercise will reduce VCAM-1, as supported by two studies (1,105). However, the study by Lara-Fernandez et al. (71) did not show any effect on VCAM-1 by aerobic exercise in patients with CAD (Table 2). There is substantial evidence that aerobic exercise decreases ICAM-1 (1,105) (Table 2). It is still a matter of debate whether exercise training decreases the levels of E-selectin; one study of resistance training showed no effect (86). Similarly, for P-selectin, insufficient evidence exists, with conflicting results.

In subjects at risk of coronary events, two weeks of exercise training reduced circulating levels of soluble ICAM-1 (123). Likewise, in patients with heart failure, exercise training decreased the circulating levels of soluble ICAM-1 and VCAM-1 (1).This positive impact of exercise on circulating cellular adhesion molecules could be related to changes in the transcriptional regulation of these molecules induced by shear stress (4). Exercise training might also have indirect favorable effects throughout the reduction of agonists of cellular adhesion molecule synthesis such as pro-inflammatory cytokines (67), ROS (75), and, thus, the oxidation of LDL (9). Therefore, by reducing soluble adhesion molecules, which may represent the interaction between activated monocytes/macrophages and endothelial cells, exercise training might be considered an effective non-pharmacological intervention to reduce endothelial adhesiveness.

EFFECTS OF EXERCISE TRAINING ON ENDOTHELIAL PROGENITOR CELLS

Endothelial function is a balance between the level of aggression and the vascular capacity to regenerate after injury, which is closely related to the number and function of endothelial-progenitor cells (EPC) (30). EPCs are circulating bone

TABLE 2. The effect of exercise training on chemokines and adhesion molecules among patients with coronary artery disease.

First Author, Year (reference)	n	RCT	Follow-Up	Intervention	IL-8	MCP-1	sVCAM-1	sICAM-1
Adamopoulos et al., 2001 (1)	12	Yes	3 mo	Aerobic exercise training: 30 min, 5 d·wk^{-1}		↓	↓	↓
Niesser et al., 2006 (84)	32	No	3 mo	Aerobic exercise training: ≥30 min, ≥3 d·wk^{-1}	↓	↓		
Schumacher et al., 2006 (105)	197	Yes	6 mo	Lifestyle intervention with aerobic exercise training: 45 min of supervised exercise, 2 d·wk^{-1} for 15 wk, plus home-based exercise	↔	↔	↔	↔
Astengo et al., 2010 (6)	56	Yes	8 mo	Aerobic exercise training: ≥30 min, 5 d·wk^{-1}	↔			
Lara-Fernandez et al., 2011 (71)	34	Yes	16 wk	Aerobic (40 min) and resistance (10 min) exercise training: 3 d·wk^{-1}			↔	

IL-8 = Interleukin-8; RCT = randomized controlled trial; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1

marrow-derived stem cells that can differentiate into mature endothelial cells (30). If required, EPCs are mobilized from bone marrow and released into peripheral circulation. This process is regulated by several growth factors, enzymes, ligands, and cell surface receptors, as well as by the direct effect of increased blood flow within bone marrow (30). Exercise training seems to be the most effective intervention in stimulating EPC production (30). Exercise training has been reported to chronically increase the number of circulating EPCs both in healthy subjects (72) and patients with CAD (84,85). Laufs et al. (72) reported an average increase of about 300% in the circulating EPCs after 4 wk of regular exercise training. Such an increase could be partially explained by the stimulation of bone marrow as a result of local increase in the bioavailability of NO (72), in turn favoring the mobilization of EPCs (2,72,112). In addition to the upregulation of EPC generation, exercise may increase the number of circulating EPCs by decreasing the rate of EPC apoptosis (83). This decrease seems to be mediated by the inhibition of Caspase-3, an important pro-apoptotic enzyme (79). The favorable impact of exercise training on the survival, differentiation, and function of EPCs may also be indirectly ascribed to the reduction of circulating levels of CRP (104,119). Independent of the underlying mechanisms, the current knowledge supports the view that exercise is an effective tool to enhance endothelial regenerative capacity.

EFFECTS OF EXERCISE TRAINING ON MICRO-RNAS

Micro-RNAs (miRNAs) have emerged as key modulators of mammalian cardiovascular development and disease (114). Individual miRNAs modulate the expression of collections of messenger RNA targets that often have related functions, thereby regulating complex biological processes (114). Heart failure and several cardiovascular diseases are associated with a specific signature pattern of miRNAs (66,116). Several miRNAs have been shown to modulate biological pathways in skeletal and cardiac muscle hypertrophy and metabolism (26,66,97,116).

Aerobic and resistance exercise interventions alter the global transcriptional miRNAs pattern of these tissues (26,29,66,97,99,116). These changes in miRNAs expression provide numerous novel explanations for the effects of training on metabolism. For instance, an acute aerobic exercise intervention downregulates miR-23a expression in skeletal muscle in both humans and mice (85,99). miR-23a is verified as a direct target for PGC-1a, a regulator of mitochondrial biogenesis (85). The exercise-induced alteration in miRNAs expression could be more likely considered a muscular adaptation mechanism in response to endurance training.

Few studies have shown that increased physical activity is associated with altered levels of circulating miRNAs. Baggish et al. (7) demonstrated altered expression of select circulating miRNAs in response to both acute and chronic exercise interventions. Baggish et al. (7) investigated miRNAs involved in angiogenesis (miR-20a, miR-210, miR-221, miR-222, miR-328), inflammation (miR-21, miR-146a), skeletal and cardiac muscle contractility (miR-21, miR-133a), and hypoxia/ischemia adaptation (miR-21, miR-146a, and miR-210). They found that distinct patterns of miRNAs response to exercise were observed and adhered to four major profiles: (1) miRNAs upregulated by acute exercise before and after sustained training (miR-146a and miR-222), (2) miRNAs responsive to acute exercise before but not after sustained training (miR-21 and miR-221), (3) miRNAs responsive only to sustained training (miR-20a), and (4) non-responsive miRNAs (miR-133a, miR-210, miR-328). These findings thus suggest that the selected circulating miRNAs have distinct expression profiles in response to these interventions (12). Another study has demonstrated that low maximal aerobic oxygen consumption is associated with high expression levels of three different circulating miRNAs (25).

There are limited studies that report the involvement of miRNAs in cardiovascular adaptive response to exercise training (31,34,110,122). In one study, swim training in rats increased cardiac expression of miR-126 expression, which is regarded as an endothelial specific miRNA supporting angiogenesis by directly repressing two negative regulators of vascular endothelial growth factor (102). Another study reported that miR-29 is involved in the improvement of ventricular compliance and is promoted by aerobic exercise training due to a modulation of decreased collagen synthesis in cardiac fibroblasts (110). Regarding the regulation of eNOS activity by increased shear stress, cell-culture experiments suggested an involvement of miRNA-21, where overexpression of the former resulted in an activation of eNOS and a 3.7-fold increased NO production, yet inhibition of miRNA-21 abolished the shear-induced activation of eNOS (122).

EFFECTS OF EXERCISE TRAINING ON OXIDATIVE STRESS

Several studies have shown ROS activation in the cardiovascular system in response to different stressors (100), and that antioxidants and ROS defense pathways can improve ROS-mediated cardiac abnormalities (50). ROS have been linked to pathologic processes such as cardiac hypertrophy (83) cardiomyocyte apoptosis (120), ischemia-reperfusion (129), and heart failure (69). ROS overproduction also occurs in response to several stimuli, including chemicals, drugs, pollutants, high-caloric diets, and exercise (10). Moreover, oxidative stress results in abnormalities in mitochondrial function, calcium handling, electrolytes alterations, hormones, and cardioprotective signaling each have been proposed as potentially implicated in the aging process (21).

It is well known that physical exercise increases ROS, eventually causing a perturbation of homeostasis that is dependent on training specificity (19) and workload (24); however, in turn, it is also able to counterbalance the deleterious effects of ROS by activation of several antioxidant systems, such as super oxide dismutases (SODs), heat shock proteins, and catalase (23). The mechanisms by which ROS mediate these different biologic responses are not fully

understood, but in many cases it involves the activation of specific redox-sensitive signaling molecules. It has been demonstrated that sirtuins, NAD+/NADH deacetylases, are involved in modulating the cellular stress response directly by deacetylation of factors also implicated in endothelial function control, and in vascular biology, regulating aspects of age-dependent atherosclerosis (22). Exercise training, although it increases ROS, is able to induce an increase in sirtuin-1 activity that, in turn, modulates the antioxidant cellular response (32).

EFFECTS OF EXERCISE TRAINING ON HIGH MOBILITY GROUP BOX-1

High mobility group box-1 (HMGB1) is a non-histone DNA binding protein involved in maintenance of nucleosome structure and active in DNA recombination, replication, and gene transcription (126). HMGB1 could be included in the family of the damage-associated molecular pattern molecules (DAMPs), known also as alarmins. The DAMPs family includes several molecules, different in their structure and sequence, released from necrotic cells, which are able to activate the innate immune system (95). HMGB1, besides being released from necrotic cells, can be secreted in extracellular medium by activated monocytes via a non-classical, vesicle-mediated secretory pathway in response to pro-inflammatory stimuli (e.g., INF-γ, LPS, TNF-α) (18). Of note, the HMGB1 secreted by activated monocytes has an acetylated tail that is not present when this protein is passively released by necrotic cells, suggesting that acetylation might play a role in modulating HMGB1 transport outside activated cells (102). Moreover, HMGB1 can be released from apoptotic cells (8). This apoptotic-derived HMGB1 is oxidized on Cys106 in a process in which Caspase activity and mitochondrial ROS are actively involved. Therefore, these data suggest that, in the pathophysiology of inflammation, HMGB1 might exert its effects as an early initiator (passive release from necrotic cells) and as a late promoter (active late release from macrophages as well as passive release) of inflammation (18).

HMGB1 has been found in atherosclerotic lesions, where it is released by activated macrophages (64) and, in turn, induces expression of other inflammatory cytokines (64), which are able to amplify macrophages recruitment starting a vicious circle (18). It has been suggested that this inflammatory cytokine-HMGB1 cycle sustains inflammation and generates a chronic inflammatory state in atherosclerotic lesions (64). HMGB1 might be involved in plaque growth, because it triggers smooth muscle cell migration and proliferation. Moreover, HMGB1 might promote progression of atherosclerosis by stimulating migration of macrophages and activation/maturation of dendritic cells (18). HMGB1 stimulates activation of endothelial cells because it upregulates expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin) (82).

Few clinical studies have been published on the potential association between myocardial ischemia and HMGB1 (5,39,40,54,70,111). Goldstein et al. (54) reported high serum HMGB1 levels in nine patients with acute coronary syndrome compared to healthy volunteers. In a pre-clinical study conducted by Andrassy et al. (5), the investigators reveal that they have unpublished data showing elevated plasma HMGB1 levels in patients on admission for a ST-elevation myocardial infarction. In the recent study by Kohno et al. (70), patients with acute myocardial infarction showed transiently increased serum HMGB1 levels within the first 7 d after admission with a peak value after 12 h. The same authors reported an association between elevated HMGB1 levels and the risk of cardiac rupture and in-hospital death (70). However, these results were only based on data from three and two patients, respectively (70). Cirillo et al. (18) showed that higher HMGB1 levels in patients with acute myocardial infarction was significantly associated with cardiopulmonary and echocardiographic outcomes such as peak oxygen consumption, left ventricular end-diastolic volume, and ejection fraction. Moreover, the same authors showed a significant association between increased circulating levels of HMGB1 and autonomic dysfunction (39). In a recent study, Sorensen et al. (111) reported elevated circulating levels of HMGB1 in patients with an ST-elevation myocardial infarction when compared with controls and a significant association between high HMGB1 levels and mortality rate in these patients.

Only one study explored the effects of exercise training on HMGB1 levels in patients following acute myocardial infarction (18,40). This randomized study showed that after 6 mo, HMGB1 levels were significantly lower in exercise trained patients compared to controls (11.7 ± 7.0 vs. 20.5 ± 15.6 ng·ml^{-1}, $p = 0.0027$, respectively). In trained patients, decreased HMGB1 levels were significantly associated with significant improvements in peak oxygen consumption, heart rate recovery, reduced left ventricular end-diastolic volume, and wall motion score index. These data highlighted the relevance of inflammatory mediators in the evolution of myocardial structure and function after acute myocardial infarction and their modulation exerted by exercise training. It could be hypothesized that HMGB1 may contribute to the pathophysiological understanding of adverse remodelling leading to heart failure by unmasking different pro-inflammatory pathways that may be involved in ischemic heart disease. Further studies are needed in order to understand the underlying mechanism(s) as well as the potential effects of drug therapy.

CLINICAL IMPLICATIONS

Exercise training is an effective therapeutic modality for improving vascular wall inflammation and endothelial dysfunction in the atherosclerotic process. The positive effects of exercise training can be explained by several mechanisms including: the increase of the bioavailability of NO and antioxidant defenses, the decrease in pro-inflammatory cytokines production by the adipose tissue, skeletal muscles, endothelial cells, blood mononuclear cells, and the increase of the regenerative capacity of endothelium. However, these mechanisms do not fully account for all pathways by which

exercise can decrease endothelial dysfunction and inflammation, and hence modulate the progression of the underlying disease progression. Future research is needed to investigate underlying novel putative mechanisms (e.g., HMGB1 proteins) explaining the beneficial effects of exercise on the inflammatory profile of patients with CAD.

Keywords: atherosclerosis, inflammation, endothelial dysfunction, exercise training

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