New insights about the putative role of myokines in the context of cardiac rehabilitation and secondary cardiovascular prevention

Domenico Di Raimondo*, Giuseppe Miceli*, Gaia Musiari, Antonino Tuttolomondo, Antonio Pinto

Dipartimento Biomedico di Medicina interna e Specialistica, University of PALERMO, Palermo, Italy

Contributions: (I) Conception and design: D Di Raimondo, G Miceli; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to the work.

Correspondence to: Domenico Di Raimondo, MD, PhD. UOC di Medicina Interna con Stroke Care, Dipartimento Biomedico di Medicina Interna e Specialistica, Università degli Studi di Palermo, Palermo, Italy. Email: domenico.diraimondo@unipa.it.

Abstract: Exercise training prevents the onset and the development of many chronic diseases, acting as an effective tool both for primary and for secondary prevention. Various mechanisms that may be the effectors of these beneficial effects have been proposed during the past decades: some of these are well recognized, others less. Muscular myokines, released during and after muscular contraction, have been proposed as key mediators of the systemic effects of the exercise. Nevertheless the availability of an impressive amount of evidence regarding the systemic effects of muscle-derived factors, few studies have examined key issues: (I) if skeletal muscle cells themselves are the main source of cytokine during exercise; (II) if the release of myokines into the systemic circulation reach an adequate concentration to provide significant effects in tissues far from skeletal muscle; (III) what may be the role carried out by muscular cytokine regarding the well-known benefits induced by regular exercise, first of all the anti-inflammatory effect of exercise. Furthermore, a greater part of our knowledge regarding myokines derives from the muscle of healthy subjects. This knowledge may not necessarily be transferred per se to subjects with chronic diseases implicating a direct or indirect muscular dysfunction and/or a chronic state of inflammation with persistent immune-inflammatory activation (and therefore increased circulating levels of some cytokines): cachexia, sarcopenia due to multiple factors, disability caused by neurological damage, chronic congestive heart failure (CHF) or coronary artery disease (CAD). A key point of future studies is to ascertain how is modified the muscular release of myokines in different categories of unhealthy subjects, both at baseline and after rehabilitation. The purpose of this review is to discuss the main findings on the role of myokines as putative mediators of the therapeutic benefits obtained through regular exercise in the context of secondary cardiovascular prevention.

Keywords: Myokines; regular exercise; cardiovascular disease (CVD); cerebrovascular disease; cardiac rehabilitation

Submitted May 03, 2017. Accepted for publication Jul 18, 2017.
doi: 10.21037/atm.2017.07.30
View this article at: http://dx.doi.org/10.21037/atm.2017.07.30

Introduction

Regular physical activity protects against several pathologic conditions, the main of which are type 2 diabetes, cardiovascular diseases (CVD), colon cancer, breast cancer, and dementia (1). Recently, it has been proposed that the protective effects of physical activity could also be attributed to the muscular production of various peptide mediators called myokines. Once they are secreted during skeletal muscle contraction, they may carry out autocrine, paracrine and endocrine activities triggering specific metabolic pathways in different tissue and organs far from the muscle

such as visceral fat, bone, liver, and nervous system, among others (1-4).

Since skeletal muscle represents the most extended organ in the human body, the identification of myokines is an important finding and may provide a biochemical explanation in recognizing molecular mechanisms that provide health beneficial effects in chronic disorders associated with systemic low-level inflammation (1,5).

Sedentary life has a higher prevalence than that of all other cardiovascular modifiable risk factors (6,7). In recent times, the profits of regular exercise were extended to subjects with established CVD as a treatment option to improve the natural history of the disease in secondary prevention (8,9). This was a revolutionary changing of view because, for a long time, physical rest had been prescribed for patients with CVD.

Numerous biological effects are considered responsible for the primary and secondary prevention of CVD and for the reduction in the rate of death and inability associated with routine exercise. In fact, regular physical activity has been demonstrated to reduce abdominal adiposity and improve weight control (10-12), reduce triglyceride levels, increase high-density lipoprotein (HDL) cholesterol levels and decrease low-density lipoprotein (LDL)-to-HDL ratios (10,13), ameliorate glucose homeostasis and insulin sensitivity (14), lower blood pressure (BP) (15,16), improve autonomic tone (17,18), balance blood coagulation (19,20), augment coronary blood flow (21), improve cardiac function (22,23) and enhance endothelial function (24-26). Moreover, physical activity seems to play a fundamental role in the primary and secondary prevention of CVD modulating chronic inflammation as demonstrated by high circulating levels of inflammatory mediators that have been shown to be directly associated with most of the chronic diseases (1,27).

Regular exercise is also associated with improved psychological wellness through the reduction of stress, anxiety, and depression (10,28,29). Psychological health is recognized to be important for the prevention and management of CVD.

Finally, findings for the improvements of physical activity in the treatment and rehabilitation of subjects with chronic CVD should be based on well-designed randomized controlled trials (RCTs) (30). Up until now, a large number of RCTs studying the therapeutic role of physical activity in specific chronic disease has been accomplished allowing systematic reviews and meta-analyses. The intent of this paper is to analyze, review and discuss the present findings on the role of myokines as putative mediators of the therapeutic benefits obtained in the main CVD: essential hypertension, chronic heart failure (HF), coronary artery disease (CAD) and in the cerebrovascular diseases after regular physical activity or specific rehabilitation programs.

Myokines expression and secretion by skeletal muscle cells

Many excellent reviews have tried to summarize the findings that skeletal muscle represents a secretory organ (2,31-34), having the capacity to release hundreds of myokines, and the possible clinical implications of this evidence. Currently myokines are defined as proteins produced by skeletal muscle that are not necessarily induced by exercise nor do they have to have a systemic function but only work with a paracrine or autocrine mechanism (2,35). In order to underline the concept that not all the myokines have the same clinical relevance, some authors support the alternative definition of "exercise factors", referring to a subgroup of myokines released by skeletal muscle in response to exercise and that is secreted into the circulation working in a "hormone-like" manner (2,36). For the purpose of this review, the list of the myokines potentially involved is much more limited, in fact, the greater part of the myokines identified to date is the result of the secretome analysis over human muscle biopsies collected before and after acute exercise (37) often lacking concrete confirmations of any clinical effect. The main myokines of which we discuss in this review are interleukin (IL)-6, IL-8, IL-15, brain-derived neurotrophic factor (BDNF), monocyte chemotactic protein 1 (MCP1) and myostatin. These are the only molecules which we have enough information in unhealthy subjects in the context of cardiac rehabilitation and secondary cardiovascular prevention.

It should be underlined that any variation of the gene expression of the muscular production and/or of the plasmatic release of the myokines after exercise is generally dependent on the combination of mode, intensity, and duration of exercise (38) and that often is impossible to ascertain that a molecule identified as a myokine is of exclusive production of skeletal muscle (2).

The prototype myokine, IL-6, seems to be mostly responsible for a strong metabolic activity during exercise, by ensuring that enough fuel gets to the contracting muscle during exercise. Several works during last decades have

demonstrated that IL-6 is expressed by both types I and II muscle fibers in response to muscle contraction. When released by skeletal muscle, IL-6 operates locally to signal through gp130Rβ/IL-6Rα, determining the stimulation of 5' adenosine monophosphate-activated protein kinase (AMPK) and/or PI3-kinase to enhance glucose uptake and fat oxidation. IL-6 may also play an endocrine role to increase hepatic glucose synthesis during physical activity or lipolysis in adipose tissue (33). IL-6 is greatly generated and released after physical activity when circulating insulin levels are elevated but, on the other hand, IL-6 has also shown to be associated with obesity and decreased insulin action.

Numerous works found that IL-6 plasma concentration is enhanced in patients with unstable angina in comparison with those with stable angina or healthy subjects and that it may be helpful as a prognostic marker of CVD outcome (39), increases the risk of future myocardial infarction (40) and has been associated with CVD mortality (41). IL-6 also has been supposed to promote atherosclerosis by increasing the endothelial synthesis of chemokines and adhesion molecules, enhancing endothelial dysfunction and stimulating coagulation (42,43). In some studies IL-6 is considered as a sensor in the muscle, being released when the local glycogen concentration is low. It is plausible that a large number of IL-6, derived from muscle, reaching the circulation, may act as a hormone determining mobilization of extracellular substrates and/or to increased substrate delivery during exercise (44). During acute physical activity, in addition to high circulating concentration of IL-6, other myokines are often detectable such as IL-1 receptor antagonist (IL-1 ra), IL-10, soluble TNF-receptor (sTNF-R) (with prevalent anti-inflammatory properties), IL-8 and IL-15.

A very limited number of papers tried to ascertain the effect of regular exercise training on IL-6 levels. In patients with chronic HF, regular exercise training is reported to decrease the expression of skeletal muscle IL-6 mRNA (45), although the basal IL-6 levels of this category of patients are higher than healthy age- and sex-matched controls. Conflicting results have been obtained in subjects with coronary heart disease (CHD), comparing IL-6 plasma levels before and after training. The skeletal muscle is a major contributor to IL-6 in the circulation (46); there is only moderate evidence that regular training will decrease plasmatic levels of IL-6 (45,47,48), but is reasonable to hypothesize that during acute exercise increased levels of IL-6 serve to sustain muscular and not-muscular metabolism (IL-6 also augments hepatic glucose and increases adipose tissue fatty acid release) whereas after regular exercise the genomic adaptation to training makes less necessary the role of IL-6, whose circulating levels are in fact reduced, and in order to avoid the disadvantageous effects of a chronic elevation of IL-6, is moreover promoted the clearance of this cytokine through the hepatosplanchnic blood flow.

IL-15 is a myokine synthesized in human skeletal muscle, and has been shown to have an anabolic effect on muscle growth, and also to play a role in lipid metabolism (49). Recently, it was demonstrated that IL-15 mRNA concentration was upregulated in human skeletal muscle following physical activity (50), suggesting that IL-15 could reach high levels within the muscle after regular exercise. Furthermore, there is a negative association between plasma IL-15 levels and fat mass (51).

BDNF is a neurotrophin involved in regulating growth and survival of existing neurons (52), and also growth and differentiation of new neurons and synapses, playing an active role in learning and memory (53-57). Various lines of evidence reported low levels of circulating BDNF in individuals affected by both obesity and type 2 diabetes (58) as well as in several chronic neurological diseases (Alzheimer's disease, major depression, impaired cognitive function). BDNF mRNA and protein synthesis were upregulated in human skeletal muscle after physical activity or after electrical stimulation; unfortunately, to date, no study has been able to find muscle-derived BDNF into the circulation. BDNF appears to be a myokine working only with autocrine or paracrine action determining powerful effects on peripheral metabolism [for example, fat oxidation with a consequent effect on the amount of adipose tissue (59)].

MCP1 is a chemokine released into the bloodstream from skeletal muscle after specific types of exercise such as marathon running or high-duration resistance exercise (60). The systemic role in the release of this pro-inflammatory mediator after acute high-intensity endurance training is debated, being possibly merely linked to an acute skeletal muscle injury (61). After chronic training the behavior of plasmatic MCP1 is similar to IL-6, IL-8 and other pro-inflammatory and pro-atherosclerotic mediators: decrease. This finding has been reported in various categories of unhealthy subjects such as patients with metabolic syndrome (62), subjects with chronic HF (63), persons with CAD (64).

Myostatin is a molecule of great interest expressed by skeletal muscle because of its potential therapeutic role. It is a released ligand of growth and differentiation factors belonging to the transforming growth factor (TGF) superfamily. Several lines of research suggest that myostatin may be involved in the regulation of muscle mass (65,66) through its autocrine and paracrine effects once it has reached an appropriate concentration into the circulation (67). Myostatin has been shown to have a role also in the crosstalk between skeletal muscle and adipose tissue and may exert an effect on insulin sensitivity (68), although it has been recognized to have not a direct effect on adipocytes function and metabolism. However, an enhanced concentration of myostatin in muscle mass provokes to a higher energy amount, increased lipid uptake, and more active metabolism, reducing the volume of adipose tissue (69). Myostatin, acting as a key regulator of skeletal muscle mass, is elevated in advanced stages of chronic HF, possibly acting as a mediator of cardiac cachexia. Lenk *et al.* reported that 12 weeks of exercise training may induce a significant reduction of myostatin in skeletal muscle, demonstrating the reversibility of the muscle wasting in chronic HF (70). Higher levels of myostatin than controls have been found also in patients with chronic diseases associated with decreased mobility, inflammation, and weight loss such as chronic obstructive pulmonary disease (COPD) (71,72) or end-stage chronic kidney disease (CKD) undergoing to hemodialysis (73).

The list of myokines is steadily increasing over the years; several of which potentially of interest. Fibroblast growth factor (FGF)-21, is a member of the FGF family involved in carbohydrate and lipid homeostasis that seems to be associated with obesity, diabetes and atherosclerotic damage (74,75).

Apelin, is an interesting insulin-related factor localized in cardiomyocytes and vascular cells that seem to play a key role in the regulation of vascular tone and cardiovascular function (76,77).

Follistatin like-1(FSTL1) is a glycoprotein that has been associated with an improved vascular health and function, counteracting endothelial dysfunction (78).

The finding that skeletal muscle during contraction expresses and releases many myokines in the circulation suggests a relationship between myokines and metabolism both in physiologic and in pathologic conditions. Since circulating markers of inflammation are chronically elevated in CVD and other vascular diseases, a change in their levels induced through physical activity may play a role in the treatment of these diseases; in the second part of this review, we tried to discuss this issue, referring to the main vascular pathologic conditions.

Arterial hypertension

The main guidelines indicate that routine exercise is considered to play a fundamental role in the prevention and treatment of hypertension (79). Several studies demonstrated that exercise is associated with a lower BP, and meta-analyses of RCTs have indicated that chronic dynamic aerobic endurance training can be effective to reduce BP levels both in normotensives and in hypertensive subjects (16,80-83). A recent meta-analysis (84) examines the effect of regular dynamic aerobic endurance exercise on resting and ambulatory BP, on BP-regulating mechanisms, and on concomitant cardiovascular risk factors, like body fatness, waist circumference, blood lipids, and glucose/insulin dynamics, finding beneficial effects of exercise in all outcomes and concomitant risk factors. They recognized that the BP decline was most evident in the hypertensive study groups, but a good BP reduction may also be found in normotensive and pre-hypertensive subjects (85). A reduction in the activity of the autonomic nervous system is supposed to be involved in the decrease of BP after exercise, as demonstrated by the 29% lower plasma norepinephrine levels in trained subjects when compared with unfit counterparts. Interestingly, some studies recognized a lack of an effect on BP during sleep (86), when sympathetic activity is reduced, that may be compatible with the hypotensive effect of the sympathetic nervous system after regular exercise. The 20% decrease of plasma renin activity suggests the role of the renin-angiotensin system (87,88). Moreover, the decreased level of plasma renin activity supports the hypothesis that the reduction in the activity of the sympathetic nervous system also affects the kidney, which is the most potent factor involved in long-term BP regulation (89). Another import role in the exercise-induced reduction of BP levels is played also by the consequent reduction of insulin resistance and improvement of the endothelial function obtained through regular training (1).

Other studies conducted with untreated patients with mild essential hypertension who walked quickly for 30 minutes 5 to 7 times per week for 12 weeks found a reduction in systolic and diastolic BPs and an augmented forearm blood flow in response to acetylcholine infusion.

This increased blood flow seems blocked by a nitric oxide (NO) inhibitor (90), suggesting a role for NO. Sedentary hypertensive rats seem to have augmented adrenergic agent-induced vasoconstricting responses, associated with reduced NO expression, of thoracic aortas and carotid arteries compared with exercise-trained hypertensive rats (91). Moreover, plasma nitrate (an index of NO quantity) was decreased in sedentary hypertensive rats compared with allowed access to 35 days of voluntary wheel running (92). Interestingly, this effect persists for 36 h, but exercised rats returned to sedentary levels by the 7th day of detraining.

The most validated mechanism supposed to lower BP through physical activity contemplates the synergism of both vascular and neurohumoral systems that determine a reduction in total peripheral resistance and catecholamines level (93). A comprehensive study of the benefits that exercise exerts on BP is very complicated since physical activity is involved in many other different effects like lipid and glucose control, weight loss, improved endothelial function and enhanced antioxidant capacity. Some data suggest that a genetic link is present between the grade of BP reduction and acute and chronic exercise in accord to the variability of results in individuals that was encountered (94). Moreover, angiotensin-converting enzyme (ACE), apolipoprotein E (apoE), and lipoprotein lipase (LPL) genotypes can be found in hypertensive subjects whose BP and cardiovascular risk can be markedly reduced with regular exercise. These genotype-dependent responses can support the hypothesis that endurance physical activity can lead to a more significant improvement of BP and circulating lipid levels in genetically advantaged subjects. Despite this significant amount of evidence supporting the role of regular exercise in improving the BP profile both in normotensive and in hypertensive subjects, to date no studies addressed the issue of the possible role carried out by myokines in causing these beneficial effects. Future studies are needed to clarify this topic.

Cerebrovascular disease

Neuroinflammation represents a key mechanism during both the acute phase of an ischemic stroke and in the recovery phase during the post-stroke rehabilitation. The level of systemic inflammation in stroke patients strongly depends on the diagnostic subtype of stroke and is directly related to the extent of the neurological damage during the acute phase and to the residual disability (95-101). Following neurological rehabilitation, usually initiated early as possible after the clinical stabilization, various authors demonstrated the change of plasma concentrations of different circulating mediators, whose role is under investigation. An increase of the plasmatic levels of the most famous neurotrophic factor, BDNF, has been demonstrated after acute aerobic exercise in an intensity-dependent manner both in healthy subjects (102,103) and in multiple sclerosis patients (104). The main origin of exercise-induced circulating BDNF is likely to be the brain rather than the muscle (specific areas of the human brain such as the hippocampus and cerebral cortex) (103,105). Nevertheless with the uncertainty regarding the main source, exercise-induced BDNF may be reasonably considered as an effective mediator of improved neurological health.

Another recently discovered factor associated with exercise-induced neuronal recovery after ischemic injury is the insulin growth factor (IGF)-1. Various reports indicate that IGF-1, released by various tissues including the skeletal muscle, may have a relevant role in neuroplasticity together with BDNF (106-108). IGF-1 would play an active role in mediating the recovery of neuronal function through the rehabilitation, despite an excessive release of IGF-1 is reported to have opposite effects, inducing an increased level of neuroinflammation and a worst outcome (109).

Other putative myokines having a certain neurotrophic activity are various molecules belonging to the family of the neurotrophins (110), the vascular endothelial growth factor (VEGF) (111), the neurotrophin ciliary neurotrophic factor (CNTF) (112), FGF21 (113), even if any significant muscular release of these substances after acute exercise or exercise training is far from being proven.

Congestive HF

Physical inactivity seems to play a role in the development of a great percentage of cases of congestive heart failure (CHF) and also aggravate conditions associated with previously diagnosed CHF patients. A sedentary lifestyle can account for 9.2% of all cases of CHF. Physical activity of individuals affected by moderate to severe CHF can reduce all-cause mortality by 63% and decreased hospital readmission for HF by 71% (114). Moreover, subjects with CHF improved their quality of life from participating in physical training programs (115). According to 14 RCTs, physical activity showed a physiological favorable effect in CHF patients focusing on short-term training program benefits (116). In the Cochrane systematic

review of exercise-based interventions for HF (117), the authors concluded that physical activity clearly ameliorates short-term exercise capacity. The meta-analysis by the ExTraMATCH Collaborative Group (118) found that there was no evidence that supervised exercise training programs for CHF patients were dangerous and indeed authors encountered an overall reduction in mortality.

Even if the principal affected organ in CHF is recognized to be the heart, skeletal muscle is thought to be a secondary defective organ involved in reducing exercise tolerance. Moreover, skeletal muscle dysfunction in CHF experiments great benefits with regular physical training, even if the function of the heart remains unaffected by exercise. In many HF subjects, the limitation in skeletal muscle function is more predominant than the hemodynamic impairment due to the cardiac dysfunction (119). In these patients the reduction of the functional capacity may lead to a progressive reduction of the mobility; this condition has shown to increase the risk of appearance of other chronic diseases. The worsening of the health status due to the multiple comorbidities causes further exercise restriction and increased hospitalization and mortality in individuals with symptomatic HF (119). It is recognized that the reductions in physical capacity in CHF are not just secondary to alterations in myocardial function (120). In fact, some indexes of cardiac function like ejection fraction are not improved by exercise in CHF patients (121). On the other hand, exercise capacity does correlate greatly with measures of peripheral muscular strength and endurance which explain the exercise intolerance in CHF patients with cellular alterations in the periphery (122). An interesting study (123) showed that 4–6 months of aerobic training in CHF subjects ameliorate exercise capacity and increase blood flow to the peripheral musculature. These muscular changes are accompanied by a decreased skeletal muscle expression of tumor necrosis factor -alpha, IL-1-beta, and IL-6 (45), with the following reduction of systemic inflammation in these patients.

The precise mechanisms through which regular physical activity determines its positive effect in patients with HF remains not completely clear. Certainly, the significant clinical improvement obtained through the regular training in CHF patients is the result of a complex interplay of different effects:

(I) Improved cardiopulmonary efficiency and pulmonary functional capacity (124);
(II) Amelioration of myocardial perfusion in ischemic subjects by reducing endothelial dysfunction and by inducing new vessel formation by way of intermittent ischemia (118);
(III) Improved myocardial contractility and diastolic filling (125);
(IV) Counteract the muscle wasting and cachexia. Myostatin may be involved in the pathophysiology of cardiac progressive dysfunction in chronic HF. In the already cited study of Lenk *et al.* (70), chronic HF subjects at baseline showed a two-fold increase of myostatin mRNA ($P=0.05$) and a 1.7-fold ($P=0.01$) augmentation of protein content in skeletal muscle compared to healthy subjects. Also in animal models, myostatin seems to be involved: myocardial gene and protein expression are increased in response to chronic volume overload-induced by aortocaval shunt in rats (126) and after acute myocardial infarction in rat cardiomyocytes (127);
(V) Reduction of the systemic inflammation;
(VI) Attenuation of the sympathoexcitation, a typical feature of CHF, helping to restore autonomic balance to the heart even in the persistence of cardiac dysfunction (128);
(VII) Modulation of the cardiac angiotensin receptor, with a secondary restoration of the overactivated renin-angiotensin-aldosterone system (129).

CAD

Many interesting papers have suggested a positive effect of physical activity on coronary vasodilation and endothelial function. Animal studies have largely demonstrated that physical activity determines a flow-mediated epicardial coronary vasodilation that seems to be dependent upon the integrity of the endothelium (130,131).

As we have already discussed, hypertension seems to be associated with decreased expression and/or augmented degradation of vascular NO (132), causing a reduction in vessel vasodilation. The altered availability of vascular NO, expression of endothelial dysfunction, is also involved in the progress of atherosclerosis. Physical activity increases NO expression in endothelial cells (21,133). Vasodilation secondary to exercise training is supposed to be mediated by shear stress (134). In fact, when in studies where fluid flow was increased in culture, endothelial cells register an augmentation of NOS mRNA (135). The augmented levels of NO stimulate vasodilation, which then lessens the enhancing in shear stress across an endothelial cell.

Numerous systematic reviews have shown the fundamental role played by regular training to attenuate or reverse the disease process in patients with CAD. For instance, a systematic review and meta-analysis involving 48 clinical trials (136) indicated that, compared with usual care, cardiac rehabilitation determine a marked reduction of incidence of premature death from any cause and from CVD in particular. In another systematic review, RCTs show that physical activity in documented CHD decrease all-cause mortality by 27% and total cardiac mortality by 31%, but not the rate of non-fatal myocardial infarction (9).

Milani *et al.* conducted the first studies elucidating the benefits of physical activity and cardiovascular rehabilitation on the plasma levels of C-reactive protein (CRP). They encountered a great reduction in CRP after the 3-month intervention in CAD patients with and without metabolic syndrome (137), in weight gainers and losers (138), and in subjects with or without statin therapy (138). These findings were confirmed by other studies (139-141). An important study (142), assessing the results of aerobic exercise training on concentrations of pro- and anti-inflammatory cytokines, IL-1, IL-6, IL-10, INF-gamma, and CRP in CAD subjects attending a cardiac rehabilitation program demonstrated a consistent reduction of CRP levels after 12 weeks of training, along with a significant decrease of all pro-inflammatory cytokines, IL-1, IL-6, interferon-gamma and a great increase in the main anti-inflammatory cytokine: IL-10 (142). In another study (140) after 24 months of exercise, CRP concentration was reduced by 41% and IL-6 levels by 18 % but no change was observed in the percutaneous intervention group. Furthermore, these findings indicate that cardiac rehabilitation and physical activity exert an anti-inflammatory effect independent of statin therapy and weight loss. Similarly, in patients with CAD, 6 months of routine exercise showed an important decrease of IL-6 and other pro-inflammatory cytokines (143). Conversely, Astengo *et al.* in 62 individuals with stable angina followed for 8 months before and after the intervention of percutaneous coronary intervention (PCI) with a training program that consisted of home-based training on a bicycle ergometer did not find any modifications of plasmatic concentration of pro-inflammatory or anti-inflammatory cytokines (IL-6, IL-8, and IL-10) (144). Niessner *et al.* (64) evaluated the benefits of endurance exercise on atherosclerosis inflammatory markers in patients with CAD and cardiovascular risk factors. In this study, after a training intervention period of 12 weeks, authors encountered a great reduction of the chemokines IL-8, monocyte chemoattractant protein-1 and of matrix metalloproteinase-9 (MMP-9), that markedly reduced after training, but an insignificant modification of IL-6 and hsCRP (64). These results also indirectly confirm the improved stabilization of the atherosclerotic plaque induced by regular exercise and provide an explanation for the reduced rate of vascular event exercise-related.

In a study examining 86 cardiac surgery patients after 15 days of cardiovascular rehabilitation authors encountered a significant reduction of baseline concentration of IL-8 (145), moreover 15 weeks of exercise training decreased IL-8 plasmatic levels in 27 obese subjects (146) and 12 weeks of controlled endurance exercise lowered IL-8 concentration in individuals with CAD and multiple cardiovascular risk factors (64).

The overall effect observed after cardiac rehabilitation in CHD patients seems to be a reduction of the main circulating cytokines associated with chronic inflammation. In relation to the other main myokines discussed in this review, a higher serum level of myostatin has been related to lower muscle function, given the fact that myostatin acts as a negative regulator of muscular growth. In experimental models of myocardial ischemia-related injury, it has been reported an immediate upregulation of cardiac myostatin (147). This finding allows us to hypothesize both an active role of this molecule in the ischemia-induced myocardial damage and a putative role for the inhibitors of myostatin (i.e., follistatin) induced by exercise in mediating the recovery after an acute episode of CHD.

Conclusive remarks

Everyone agreed on having to advise routine exercise among individuals with CVD; several lines of research confirm the significant benefits associated with an improved physical fitness without causing adverse effects on disease progression. Work on subjects with CAD as well as studies on individuals with CHF show that physical activity is associated with lower all-cause mortality compared with controls. Among old patients with CVD, both enhanced fitness levels and a decrease in disease-related symptoms are very important effects although several RCTs are too short to document differences in the true disease progression between groups. Although recommended characteristics of a training program ameliorating aerobic fitness are known to include at least 20 minutes of moderate-intensity training

twice a week or more during at least 6 weeks in accord to American College of Sports Medicine, in older patients with CVD there is a need of more tailored programs with a specific intensity of exercise. Low-intensity regimens are effective as high-intensity programs in different pathologic conditions such as type 2 diabetes (14) and 5 to 10 minutes of running/day also at slow speed (<6 miles/hour) has been associated with markedly reduced risk of death from all causes and CVD (148), while 92 minutes per week or 15 minutes a day of moderate intensity endurance training have been reported to provide a 14% reduced risk of all-cause mortality and 3 years longer life expectancy (149). But, on the other hand, several lines of evidence indicate that seems to be a threshold to the dose/effectiveness curve of exercise benefit: to stay on the safe side, the progression of exercise programs must be slow and tailored considering patients' ability and occurrence of different symptoms. Most of the patients seem to have a positive effect from low- to moderate-intensity exercise training. However, according to the available RCTs, final comprehensive conclusions about the kind of training or dose-response of exercise therapy in the treatment of CVD cannot be finally assessed.

The mechanisms through which regular exercise is of benefit for these categories of subjects are only partly understood. Improved overall control of the main cardiovascular risk factors, enhanced NO-mediated vasodilation and optimized shear stress are surely main benefits. Myokines exert various endocrine effects on various tissues and organs, including adipose tissue, the liver, the pancreas and the brain; mainly exerting a certain metabolic role. Acute exercise and regular training exert very different effects on muscular myokinome, with acute exercise eliciting a more stress-like response compared with a chronic adaptive response observed after habitual exercise. To date, conclusive evidence is lacking regarding a possible role exerted by myokines released into the bloodstream after exercise and acting in a hormone-like manner as mediators of the beneficial effects of exercise in patients in secondary prevention after a vascular event. Other well-known hemodynamic, immunomodulatory and anti-atherosclerotic effects of regular exercise are convincingly able to explain the epidemiologic data showed in this review. But nevertheless, molecules such as myostatin, FGF21 (150,151), apelin, and FSTL1 (152), to name just a few, are promising therapeutic agent of absolute interest. We are expecting ad hoc trials clarifying their real potential.

Regarding the putative anti-inflammatory effect of exercise, confirmed by several lines of evidence, a conclusive message may be similar: the expression of myokines from skeletal muscle is directly related to training intensity, while the anti-inflammatory effect of exercise is not. It is largely accepted that the expression of IL-6 after acute physical activity do not reach consistent concentrations with short durations or low-to-moderate intensity of training (153) and that routine physical activity determines a decrease of IL-6 levels (instead of IL-10 concentration that is shown to increase). On the other hand, many studies reported data that assess how also low-intensity programs of exercise, such as fast walking (16,27,154,155), could produce a consistent decrease in plasma markers of systemic inflammation although does not determine any enhance in circulating cytokines expression (156). These data allow us to hypothesize that other well-known mechanisms (direct and indirect modulation of the activity of immune cells, neuroendocrine changes induced by exercise, reduced fat mass, for example) could explain a great part of the anti-inflammatory effect of exercise. Moreover, in clinical practice, physical activity is not prescribed alone but rather with other lifestyle advice such as weight loss, low-fat diet, smoking cessation or also in combination with pharmacological treatments. How may coexisting treatments influence skeletal muscle myokines expression? Is there any synergic effect between drugs and exercise? Well-designed cross-sectional and longitudinal studies are needed to better explain the potentiality of exercise in the context of cardiac rehabilitation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Di Raimondo D, Musiari G, Miceli G, et al. Preventive and Therapeutic Role of Muscle Contraction Against Chronic Diseases. Curr Pharm Des 2016;22:4686-99.
2. Di Raimondo D, Tuttolomondo A, Musiari G, et al. Are the Myokines the Mediators of Physical Activity-Induced Health Benefits? Curr Pharm Des 2016;22:3622-47.

3. Brandt C, Pedersen BK. The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. J Biomed Biotechnol 2010;2010:520258
4. Peake JM, Della Gatta P, Suzuki K, et al. Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. Exerc Immunol Rev 2015;21:8-25.
5. Pinto A, Di Raimondo D, Tuttolomondo A, et al. Effects of physical exercise on inflammatory markers of atherosclerosis. Curr Pharm Des 2012;18:4326-49.
6. Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: current evidence and research issues. Med Sci Sports Exerc 1999;31:S646-62.
7. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Med Sci Sports Exerc 2001;33:S379-99.
8. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. Circulation 2000;102:1358-63.
9. Jolliffe JA, Rees K, Taylor RS, et al. Exercise-based rehabilitation for coronary heart disease. Cochrane Database Syst Rev 2001;(1):CD001800.
10. Warburton DE, Gledhill N, Quinney A. Musculoskeletal fitness and health. Can J Appl Physiol 2001;26:217-37.
11. Seidell JC, Cigolini M, Deslypere JP, et al. Body fat distribution in relation to physical activity and smoking habits in 38-year-old European men. The European Fat Distribution Study. Am J Epidemiol 1991;133:257-65.
12. Tremblay A, Despres JP, Leblanc C, et al. Effect of intensity of physical activity on body fatness and fat distribution. Am J Clin Nutr 1990;51:153-7.
13. Berg A, Halle M, Franz I, et al. Physical activity and lipoprotein metabolism: epidemiological evidence and clinical trials. Eur J Med Res 1997;2:259-64
14. Balducci S, Zanuso S, Cardelli P, et al. Effect of high- versus low-intensity supervised aerobic and resistance training on modifiable cardiovascular risk factors in type 2 diabetes; the Italian Diabetes and Exercise Study (IDES). PLoS One 2012;7:e49297
15. Di Raimondo D, Miceli G, Casuccio A, et al. Does sympathetic overactivation feature all hypertensives? Differences of sympathovagal balance according to night/day blood pressure ratio in patients with essential hypertension. Hypertens Res 2016;39:440-8.
16. Pinto A, Di Raimondo D, Tuttolomondo A, et al. Twenty-four hour ambulatory blood pressure monitoring to evaluate effects on blood pressure of physical activity in hypertensive patients. Clin J Sport Med 2006;16:238-43.
17. Adamopoulos S, Piepoli M, McCance A, et al. Comparison of different methods for assessing sympathovagal balance in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1992;70:1576-82.
18. Tiukinhoy S, Beohar N, Hsie M. Improvement in heart rate recovery after cardiac rehabilitation. J Cardiopulm Rehabil 2003;23:84-7.
19. Physical activity and cardiovascular health. NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. JAMA 1996;276:241-6.
20. Rauramaa R, Salonen JT, Seppanen K, et al. Inhibition of platelet aggregability by moderate-intensity physical exercise: a randomized clinical trial in overweight men. Circulation 1986;74:939-44.
21. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 2000;342:454-60.
22. Warburton DE, Gledhill N, Jamnik V, et al. Induced hypervolemia, cardiac function, VO2max and performance of elite cyclists. Med Sci Sports Exerc 1999;31:800-8.
23. Warburton DE, Haykowsky MJ, Quinney HA, et al. Blood volume expansion and cardiorespiratory function: effects of training modality. Med Sci Sports Exerc 2004;36:991-1000.
24. Gokce N, Vita JA, Bader DS, et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. Am J Cardiol 2002;90:124-7.
25. Kobayashi N, Tsuruya Y, Iwasawa T, et al. Exercise training in patients with chronic heart failure improves endothelial function predominantly in the trained extremities. Circ J 2003;67:505-10.
26. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. JAMA 2000;283:3095-101
27. Di Raimondo D, Tuttolomondo A, Buttà C, et al. Metabolic and anti-inflammatory effects of a home-based programme of aerobic physical exercise. Int J Clin Pract 2013;67:1247-53.
28. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose–response effects on outcomes of depression and anxiety. Med Sci Sports Exerc 2001;33:S587-97.
29. Pareja-Galeano H, Mayero S, Perales M, et al. Biological Rationale for Regular Physical Exercise as an Effective Intervention for the Prevention and Treatment of Depressive Disorders. Curr Pharm Des 2016;22:3764-75.
30. Kujala UM. Evidence for exercise therapy in the treatment of chronic disease based on at least three randomized

controlled trials – summary of published systematic reviews. Scand J Med Sci Sports 2004:14:339-45.
31. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 2012;8:457-65.
32. Raschke S, Eckel J. Adipo-myokines: two sides of the same coin-mediators of inflammation and mediators of exercise. Mediators Inflamm 2013;2013:320724.
33. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 2008;88:1379-406.
34. Welc SS, Clanton TL. The regulation of interleukin-6 implicates skeletal muscle as an integrative stress sensor and endocrine organ. Exp Physiol 2013;98:359-71.
35. Henningsen J, Rigbolt KT, Blagoev B, et al. Dynamics of the skeletal muscle secretome during myoblast differentiation. Mol Cell Proteomics 2010;9:2482-96.
36. Catoire M, Kersten S. The search for exercise factors in humans. FASEB J 2015;29:1615-28.
37. Catoire M, Mensink M, Kalkhoven E, et al. Identification of human exercise-induced myokines using secretome analysis. Physiol. Genomics 2014;46:256-67.
38. Nieman DC, Konrad M, Henson DA, et al. Variance in the acute inflammatory response to prolonged cycling is linked to exercise intensity. J Interferon Cytokine Res 2012;32:12-7.
39. Biasucci LM, Vitelli A, Liuzzo G, et al. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;94:874-7.
40. Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767-72.
41. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506-12.
42. Yudkin JS, Kumari M, Humphries SE, et al. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 2000;148:209-14.
43. Elhage R, Clamens S, Besnard S, et al. Involvement of interleukin-6 in atherosclerosis but not in the prevention of fatty streak formation by 17beta-estradiol in apolipoprotein E-deficient mice. Atherosclerosis 2001;156:315-20.
44. Keller C, Steensberg A, Pilegaard H, et al. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. FASEB J 2001;15:2748-50.
45. Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J Am Coll Cardiol 2003;42:861-8.
46. Steensberg A, Van Hall G, Osada T, et al. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. J Physiol 2000;529:237-42.
47. Palmefors H, DuttaRoy S, Rundqvist B, et al. The effect of physical activity or exercise on key biomarkers in atherosclerosis--a systematic review. Atherosclerosis 2014;235:150-61.
48. Kadoglou NP, Perrea D, Iliadis F, et al. Exercise reduces resistin and inflammatory cytokines in patients with type 2 diabetes. Diabetes Care 2007;30:719-21.
49. Nielsen AR, Pedersen BK. The biological roles of exercise-induced cytokines: IL-6, IL-8, and IL-15. Appl Physiol Nutr Metab 2007;32:833-9.
50. Nielsen AR, Mounier R, Plomgaard P, et al. Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. J Physiol 2007;584:305-12.
51. Nielsen AR, Hojman P, Erikstrup C, et al. Association between interleukin-15 and obesity: interleukin-15 as a potential regulator of fat mass. J Clin Endocrinol Metab 2008;93:4486-93.
52. Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci 2004;27:589-94.
53. Tyler WJ, Alonso M, Bramham CR, et al. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem 2002;9:224-37.
54. Laske C, Stransky E, Leyhe T, et al. Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm (Vienna) 2006;113:1217-24.
55. Karege F, Perret G, Bondolfi G, et al. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 2002;109:143-8.
56. Komulainen P, Pedersen M, Hänninen T, et al. BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA Study. Neurobiol Learn Mem 2008;90:596-603.
57. Krabbe KS, Mortensen EL, Avlund K, et al. Brain-derived neurotrophic factor predicts mortality risk in older women. J Am Geriatr Soc 2009;57:1447-52.
58. Krabbe KS, Nielsen AR, Krogh-Madsen R, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes.

Diabetologia 2007;50:431-8.
59. Pedersen BK, Pedersen M, Krabbe KS, et al. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. Exp Physiol 2009;94:1153-60.
60. Mathers JL, Farnfield MM, Garnham AP, et al. Early inflammatory and myogenic responses to resistance exercise in the elderly. Muscle Nerve 2012;46:407-12.
61. Pillon NJ, Bilan PJ, Fink LN, et al. Cross-talk between skeletal muscle and immune cells: muscle-derived mediators and metabolic implications. Am J Physiol Endocrinol Metab 2013;304:E453–E65.
62. Roberts CK, Won D, Pruthi S, et al. Effect of a short-term diet and exercise intervention on oxidative stress, inflammation, MMP-9, and monocyte chemotactic activity in men with metabolic syndrome factors. J Appl Physiol (1985) 2006;100:1657-65.
63. Adamopoulos S, Parissis J, Kroupis C, et al. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J 2001;22:791-7.
64. Niessner A, Richter B, Penka M, et al. Endurance training reduces circulating inflammatory markers in persons at risk of coronary events: impact on plaque stabilization? Atherosclerosis 2006;186:160-5.
65. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997;387:83-90.
66. Lee SJ, McPherron AC. Regulation of myostatin activity and muscle growth. Proc Natl Acad Sci USA 2001;98:9306-11.
67. Elliott B, Renshaw D, Getting S, et al. The central role of myostatin in skeletal muscle and whole body homeostasis. Acta Physiol (Oxf) 2012;205:324-40.
68. Argilés JM, Orpí M, Busquets S, et al. Myostatin:more than just a regulator of muscle mass. Drug Discov Today 2012;17:702-9.
69. Allen DL, Hittel DS, McPherron AC. Expression and function of myostatin in obesity, diabetes, and exercise adaptation. Med Sci Sports Exerc 2011;43:1828-35.
70. Lenk K, Erbs S, Höllriegel R, et al. Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. Eur J Prev Cardiol 2012;19:404-11.
71. Ju CR, Chen RC. Serum myostatin levels and skeletal muscle wasting in chronic obstructive pulmonary disease. Respir Med 2012;106:102-8.
72. Remels AH, Gosker HR, Langen RC, et al. The mechanisms of cachexia underlying muscle dysfunction in COPD. J Appl Physiol (1985) 2013;114:1253-62.
73. Han DS, Chen YM, Lin SY, et al. Serum myostatin levels and grip strength in normal subjects and patients on maintenance haemodialysis. Clin Endocrinol (Oxf) 2011;75:857-63.
74. Chavez AO, Molina-Carrion M, Abdul-Ghani MA, et al. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. Diabetes Care 2009;32:1542-6.
75. Kliewer SA, Mangelsdorf DJ. Fibroblast growth factor 21: from pharmacology to physiology. Am J Clin Nutr 2010; 91:254S-7S.
76. Carpéné C, Dray C, Attané C, et al. Expanding role for the apelin/APJ system in physiopathology. J Physiol Biochem 2007;63:359-73.
77. Quazi R, Palaniswamy C, Frishman WH. The emerging role of apelin in cardiovascular disease and health. Cardiol Rev 2009;17:283-86.
78. Görgens SW, Raschke S, Holven KB, et al. Regulation of follistatin-like protein 1 expression and secretion in primary human skeletal muscle cells. Arch Physiol Biochem 2013;119:75-80.
79. Mancia G, Fagard R, Narkiewicz K, et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281-357.
80. Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. Eur J Cardiovasc Prev Rehabil 2007;14:12-7.
81. Lee LL, Watson MC, Mulvaney CA, et al. The effect of walking intervention on blood pressure control: a systematic review. Int J Nurs Stud 2010;47:1545-61.
82. Cornelissen VA, Buys R, Smart NA. Endurance exercise beneficially affects ambulatory blood pressure: a systematic review and meta-analysis. J Hypertens 2013;31:639-48.
83. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013;2:e004473.
84. Cornelissen VA, Goetschalckx K, Verheyden B, et al. Effect of endurance training on blood pressure regulation, biomarkers and the heart in subjects at a higher age. Scand J Med Sci Sports 2011;21:526-34.
85. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating

mechanisms, and cardiovascular risk factors. Hypertension 2005;46:667-75.
86. Di Raimondo D, Tuttolomondo A, Miceli S, et al. Aerobic physical activity based on fast walking does not alter blood pressure values in non-dipper essential hypertensives. Int Angiol 2012;31:142-9.
87. Fagard RH, Tipton CM. Physical activity, fitness and hypertension. In: Bouchard C, Shephard RJ, Stephens T. editors. Physical Activity, Fitness and Health. Champaign, Ill: Human Kinetics,1994:633-55.
88. Kohno K, Matsuoka H, Takenaka K, et al. Renal depressor mechanisms of physical training in patients with essential hypertension. Am J Hypertens 1997;10:859-68.
89. Guyton AC. Kidneys and fluids in pressure regulation. Hypertension 1992;19:I2-I8.
90. Higashi Y, Sasaki S, Kurisu S, et al. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. Circulation 1999;100:1194-202.
91. Chen HI, Chiang IP. Chronic exercise decreases adrenergic agonist-induced vasoconstriction in spontaneously hypertensive rats. Am J Physiol 1996;271:H977-83.
92. Jonsdottir IH, Jungersten L, Johansson C, et al. Increase in nitric oxide formation after chronic voluntary exercise in spontaneously hypertensive rats. Acta Physiol Scand 1998;162:149-53.
93. Pescatello LS, Franklin BA, Fabard R, et al. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 2004;36:533-53.
94. Hagberg JM, Ferrell RE, Dengel DR, et al. Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. Hypertension 1999;34:18-23.
95. Tuttolomondo A, Casuccio A, Della Corte V, et al. Endothelial function and arterial stiffness indexes in subjects with acute ischemic stroke: Relationship with TOAST subtype. Atherosclerosis 2017;256:94-9.
96. Della Corte V, Tuttolomondo A, Pecoraro R, et al. Inflammation, Endothelial Dysfunction and Arterial Stiffness as Therapeutic Targets in Cardiovascular Medicine. Curr Pharm Des 2016;22:4658-68.
97. Tuttolomondo A, Pecoraro R, Casuccio A, et al. Peripheral frequency of CD4+ CD28- cells in acute ischemic stroke: relationship with stroke subtype and severity markers. Medicine (Baltimore) 2015;94:e813.
98. Tuttolomondo A, Pecoraro R, Di Raimondo D, et al. Immune-inflammatory markers and arterial stiffness indexes in subjects with acute ischemic stroke with and without metabolic syndrome. Diabetol Metab Syndr 2014;6:28.
99. Tuttolomondo A, Pecoraro R, Di Raimondo D, et al. Stroke subtypes and their possible implication in stroke prevention drug strategies. Curr Vasc Pharmacol 2013;11:824-37.
100. Tuttolomondo A, Di Raimondo D, Pecoraro R, et al. Inflammation in ischemic stroke subtypes. Curr Pharm Des 2012;18:4289-310.
101. Tuttolomondo A, Pedone C, Pinto A, et al. Predictors of outcome in acute ischemic cerebrovascular syndromes: The GIFA study. Int J Cardiol 2008;125:391-6.
102. Knaepen K, Goekint M, Heyman EM, et al. Neuroplasticity: exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 2010;40:765-801.
103. Seifert T, Brassard P, Wissenberg M, et al. Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol 2010;298:R372-7.
104. Gold SM, Schulz KH, Hartmann S, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol 2003;138:99-105.
105. Rasmussen P, Brassard P, Adser H, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 2009;94:1062-9.
106. Ploughman M, Austin MW, Glynn L, et al. The effects of poststroke aerobic exercise on neuroplasticity: a systematic review of animal and clinical studies. Transl Stroke Res 2015;6:13-28.
107. Austin MW, Ploughman M, Glynn L, et al. Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. Neurosci Res 2014;87:8-15.
108. Mang CS, Campbell KL, Ross CJ, et al. Promoting neuroplasticity for motor rehabilitation after stroke: considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. Phys Ther 2013;93:1707-16.
109. Okazaki H, Beppu H, Mizutani K, et al. Changes in serum growth factors in stroke rehabilitation patients and their relation to hemiparesis improvement. J Stroke Cerebrovasc Dis 2014;23:1703-8.
110. Pasarica D, Gheorghiu M, Topârceanu F, et al.

Neurotrophin-3, TNF-alpha and IL-6 relations in serum and cerebrospinal fluid of ischemic stroke patients. Roum Arch Microbiol Immunol 2005;64:27-33.
111. Pikula A, Beiser AS, Chen TC, et al Serum brain-derived neurotrophic factor and vascular endothelial growth factor levels are associated with risk of stroke and vascular brain injury: Framingham Study. Stroke 2013;44:2768-75.
112. Kang SS, Keasey MP, Arnold SA, et al. Endogenous CNTF mediates stroke-induced adult CNS neurogenesis in mice. Neurobiol Dis 2013;49:68-78.
113. Xiao Y, Liu L, Xu A, et al. Serum fibroblast growth factor 21 levels are related to subclinical atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:72.
114. Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173-82.
115. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.
116. Lloyd-Williams F, Mair FS, Leitner M. Exercise training and heart failure: a systematic review of current evidence. Br J Gen Pract 2002:52:47-55.
117. Rees K, Taylor RS, Singh S, et al. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2004;(3):CD003331.
118. Piepoli MF, Davos C, Francis DP, et al. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189.
119. Tavazzi L, Giannuzzi P. Physical training as a therapeutic measure in chronic heart failure: time for recommendations. Heart 2001;86:7-11.
120. Volterrani M, Clark AL, Ludman PF, et al. Predictors of exercise capacity in chronic heart failure. Eur Heart J 1994;15:801-9.
121. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33-9.
122. Minotti JR, Christoph I, Oka R, et al. Impaired skeletal muscle function in patients with congestive heart failure. Relationship to systemic exercise performance. J Clin Invest 1991;88:2077-82.
123. Sullivan MJ, Green HJ, Cobb FR. Altered skeletal muscle metabolic response to exercise in chronic heart failure. Relation to skeletal muscle aerobic enzyme activity. Circulation 1991;84:1597-607.
124. Panagopoulou N, Karatzanos E, Dimopoulos S, et al. Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure. Eur J Prev Cardiol 2017;24:825-32.
125. Belardinelli R, Georgiou D, Ginzton L, et al. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation 1998;97:553-61.
126. Shyu KG, Lu MJ, Wang BW, et al. Myostatin expression in ventricular myocardium in a rat model of volume-overload heart failure. Eur J Clin Invest 2006;36:713-9.
127. Sharma M, Kambadur R, Matthews KG, et al. Myostatin, a transforming growth factor-beta superfamily member, is expressed in heart muscle and is upregulated in cardiomyocytesafter infarct. J Cell Physiol 1999;180:1-9.
128. Ichige MH, Santos CR, Jordão CP, et al. Exercise training preserves vagal preganglionic neurones and restores parasympathetic tonus in heart failure. J Physiol 2016;594:6241-54.
129. Zucker IH, Schultz HD, Patel KP, et al. Modulation of angiotensin II signaling following exercise training in heart failure. Am J Physiol Heart Circ Physiol 2015;308:H781-91.
130. Berdeaux A, Ghaleb B, Dubois-Randé JL, et al. Role of vascular endothelium in exercise-induced dilation of large epicardial coronary arteries in conscious dogs. Circulation 1994;89:2799-808.
131. Niebauer J, Cooke JP. Cardiovascular effects of exercise: role of endothelial shear stress. J Am Coll Cardiol 1996;28:1652-60.
132. Li H, Förstermann U. Nitric oxide in the pathogenesis of vascular disease. J Pathol 2000;190:244-54.
133. Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. FASEB J 2000;14:1685-96.
134. Cooke JP, Tsao PS. Go with the flow. Circulation 2001;103:2773-5
135. Nishida K, Harrison DG, Navas JP, et al. Molecular cloning and characterization of the constitutive bovine aortic endothelial cell nitric oxide synthase. J Clin Invest 1992;90:2092-6
136. Taylor RS, Brown A, Ebrahim S, et al. Exercise based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682-92.
137. Milani RV, Lavie CJ. Prevalence and profile of metabolic

syndrome in patients following acute coronary events and effects of therapeutic lifestyle change with cardiac rehabilitation. Am J Cardiol 2003;92:50-4.
138. Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. J Am Coll Cardiol 2004;43:1056-61.
139. Caulin-Glaser T, Falko J, Hindman L, et al. Cardiac rehabilitation is associated with an improvement in C-reactive protein levels in both men and women with cardiovascular disease. J Cardiopulm Rehabil 2005;25:332-6.
140. Walther C, Möbius-Winkler S, Linke A, et al. Regular exercise training compared with percutaneous intervention leads to a reduction of inflammatory markers and cardiovascular events in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil 2008;15:107-12.
141. Plüss CE, Karlsson MR, Wallen NH, et al. Effects of an expanded cardiac rehabilitation programme in patients treated for an acute myocardial infarction or a coronary artery by-pass graft operation. Clin Rehabil 2008;22:306-18.
142. Goldhammer E, Tanchilevitch A, Maor I, et al. Exercise training modulates cytokines activity in coronary heart disease patients. Int J Cardiol 2005;100:93-9.
143. Schumacher A, Peersen K, Sommervoll L, et al. Physical performance is associated with markers of vascular inflammation in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil 2006;13:356-62.
144. Astengo M, Dahl A, Karlsson T, et al. Physical training after percutaneous coronary intervention in patients with stable angina: effects on working capacity, metabolism, and markers of inflammation. Eur J Cardiovasc Prev Rehabil 2010;17:349-54.
145. Cesari F, Sofi F, Caporale R, et al. Relationship between exercise capacity, endothelial progenitor cells and cytochemokines in patients undergoing cardiac rehabilitation. Thromb Haemost 2009;101:521-6.
146. Bruun JM, Helge JW, Richelsen B, et al. Diet and exercise reduce lowgrade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. Am J Physiol Endocrinol Metab 2006;290:E961-7.
147. Castillero E, Akashi H, Wang C, et al. Cardiac myostatin upregulation occurs immediately after myocardial ischemia and is involved in skeletal muscle activation of atrophy. Biochem Biophys Res Commun 2015;457:106-11.
148. Lee DC, Pate RR, Lavie CJ, et al. Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol 2014;64:472-81.
149. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011;378:1244-53.
150. Sanchis-Gomar F, Pareja-Galeano H, Mayero S, et al. New molecular targets and lifestyle interventions to delay aging sarcopenia. Front Aging Neurosci 2014;6:156.
151. Sanchis-Gomar F, Pareja-Galeano H, Santos-Lozano A, et al. A preliminary candidate approach identifies the combination of chemerin, fetuin-A, and fibroblast growth factors 19 and 21 as a potential biomarker panel of successful aging. Age (Dordr) 2015;37:9776.
152. Sanchis-Gomar F, Perez-Quilis C, Lucia A. Overexpressing FSTL1 for Heart Repair. Trends Mol Med 2016;22:353-4.
153. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc Immunol Rev 2006;12:6-33.
154. Miyashita M, Burns SF, Stensel DJ. Accumulating short bouts ofbrisk walking reduces postprandial plasma triacylglycerol concentrations and resting blood pressure in healthy young men. Am J Clin Nutr 2008;88:1225-31.
155. Murphy M, Nevill A, Neville C, et al. Accumulating brisk walking for fitness, cardiovascular risk, and psychological health. Med Sci Sports Exerc 2002;34:1468-74.
156. Markovitch D, Tyrrell RM, Thompson D. Acute moderate intensity exercise in middle-aged men has neither an anti- nor proinflammatory effect. J Appl Physiol 2008;105:260-5.

Cite this article as: Di Raimondo D, Miceli G, Musiari G, Tuttolomondo A, Pinto A. New insights about the putative role of myokines in the context of cardiac rehabilitation and secondary cardiovascular prevention. Ann Transl Med 2017;5(15):300. doi: 10.21037/atm.2017.07.30

