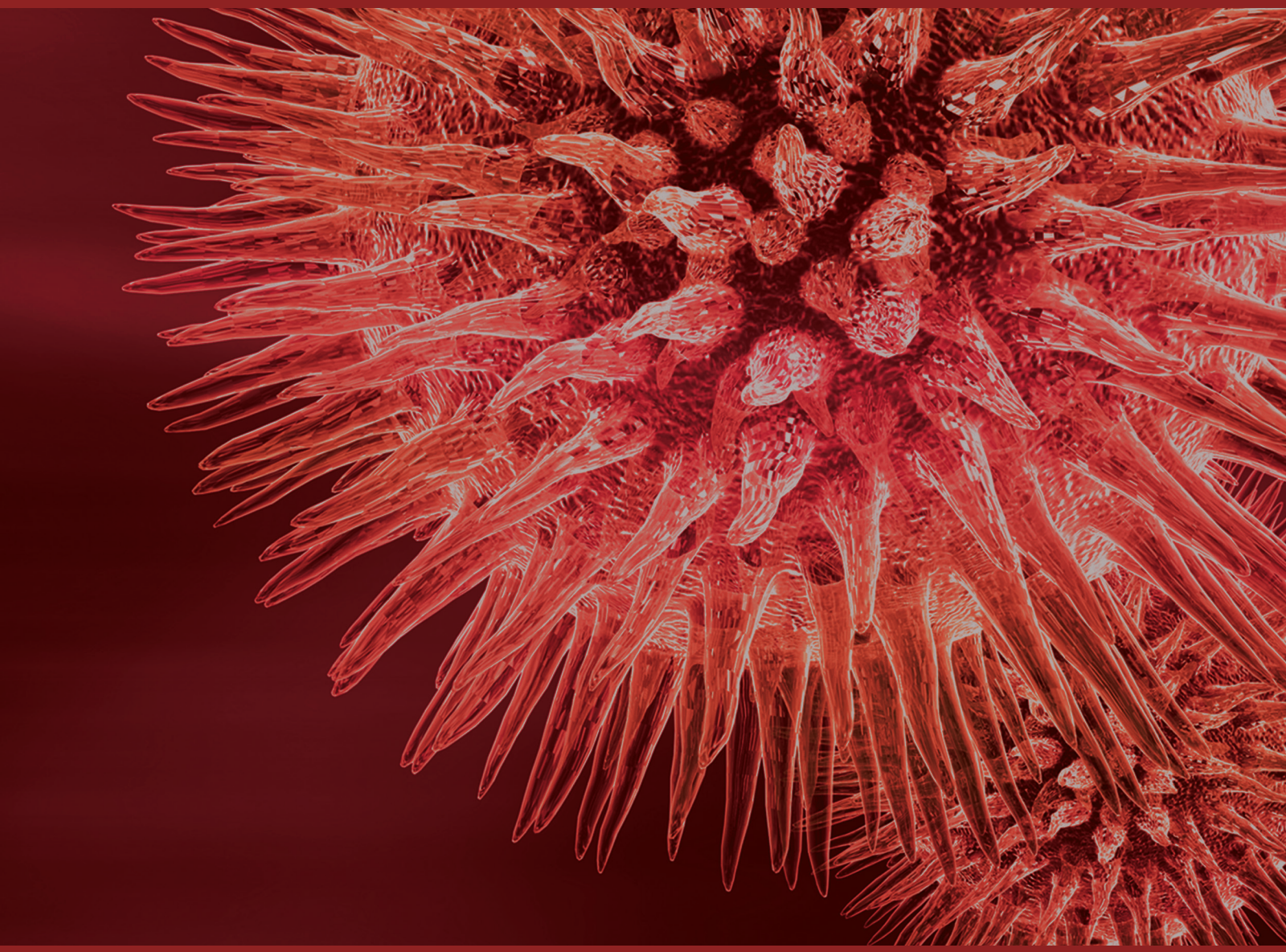
BioMed Research International

Effects of Physical Exercise on Cardiovascular Diseases: Biochemical, Cellular, and Organ Effects

Guest Editors: Antonio Crisafulli, Pasquale Pagliaro, Alain Cohen-Solal, Pier P. Bassareo, and Andrew J. Coats



Effects of Physical Exercise on Cardiovascular Diseases: Biochemical, Cellular, and Organ Effects

BioMed Research International

Effects of Physical Exercise on Cardiovascular Diseases: Biochemical, Cellular, and Organ Effects

Guest Editors: Antonio Crisafulli, Pasquale Pagliaro, Alain Cohen-Solal, Pier P. Bassareo, and Andrew J. Coats

Contents

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 853632, 2 pages
http://dx.doi.org/10.1155/2015/853632

Editorial

Effects of Physical Exercise on Cardiovascular Diseases: Biochemical, Cellular, and Organ Effects

Antonio Crisafulli,[1] Pasquale Pagliaro,[2] Alain Cohen-Solal,[3] and Andrew J. Coats[4,5]

[1]*Department of Medical Sciences, Sports Physiology Laboratory, University of Cagliari, 09124 Cagliari, Italy*
[2]*Department of Clinical and Biological Sciences, University of Torino, Torino, Italy*
[3]*Department of Cardiology, Paris Diderot University, UMR-S 942, Lariboisière Hospital, Paris, France*
[4]*Monash University, Melbourne, VIC, Australia*
[5]*University of Warwick, Coventry, UK*

Correspondence should be addressed to Antonio Crisafulli; crisafulli@tiscali.it

Received 15 October 2015; Accepted 15 October 2015

It is well recognised that regular exercise is cardioprotective. On the other hand, sedentariety is an established risk factor for cardiovascular diseases. Furthermore, several clues suggest that exercise capacity is a strong predictor of risk of death from any cause in both healthy subjects and in those with cardiovascular diseases. However, the exact mechanisms through which regular physical activity confers cardiovascular protection are not yet well understood. Exercise probably acts at multiple levels. One possibility is that regular exercise modifies genes expression, thereby changing the production of bioactive molecules such as proteins and enzymes; another potential site of action is on the mechanisms of cardiovascular regulation during effort, which are improved after periods of training; finally, exercise can affect endothelial and platelet functions, thus reducing the risks of atherosclerosis and consequently the risk of infarction and stroke.

This special issue focuses on potential beneficial mechanisms by which exercise operates to confer protection against cardiovascular diseases.

The interesting paper by S. Heber and I. Volf reviews the effects of inactivity and training on platelet functions. In their literature review, they conclude that regular physical activity diminishes or prevents platelet activation in response to acute exercise and that habitual physical activity also positively modulates platelet functions. They also conclude that these effects support the well-recognised relation between exercise and the risk for cardiovascular events, as a physically active lifestyle dramatically reduces cardiovascular mortality.

In another intriguing review, C.-Y. Hsu et al. focus on the important topic of the effects of exercise training on autonomic function in chronic heart failure (CHF). Exercise intolerance is one of the major and disturbing symptoms in these patients. Increased sympathetic tone and decreased parasympathetic activity have been often reported in CHF and these phenomena are associated with a poor survival. Data from this review indicate that participation in exercise training programs induces beneficial effects on autonomic function in CHF patients. They also point out that further research could examine additional aspects of the effects of exercise training in this population, such as the impact on the responses to exercise training in different levels of CHF severity, the possibility that a threshold intensity may be needed to affect cardiac autonomic function, and the type of exercise that should be recommended to achieve the highest positive effects on sympathovagal balance.

In a third review by A. Crisafulli et al., the complex issue of cardiovascular reflexes during exercise is addressed. During exercise, the neural mechanisms controlling the cardiovascular apparatus regulate cardiac output and arteriolar tone in order to counteract the exercise-induced vasodilation due to functional sympatholysis in the working muscle. These cardiovascular adjustments guarantee adequate perfusion to

vital organs (the brain and the heart) and to the working muscles as well as adequate washout of exercise-induced by-products. Moreover, these mechanisms prevent excessive increments in blood pressure. In this review, authors summarise neural reflexes operating during dynamic exercise, particularly their interaction. They point out that cardiovascular regulation during exercise is achieved through the contemporary integration and interaction of input arising from motor cortex (central command), skeletal muscle receptors (exercise pressor reflex), and arterial baroreceptors. They also conclude that further research is warranted to better understand how these reflexes interact during effort.

The last interesting review by R. B. Batacan Jr. et al. is about the effects of light intensity activity on cardiovascular risk factors. These authors claim that there is little support for the role of light intensity activity to reduce cardiovascular disease risk factors and that further studies are needed to establish the value of light intensity physical activity in reducing cardiovascular risk factors.

Finally, the research paper by N. G. Rocha et al. aims at evaluating the acute effects of exercise on endothelial functions in early metabolic syndrome. They find that these subjects, despite being free of symptoms, present with an early impairment of endothelial function. Moreover, they put forward the hypothesis that the analysis of some biomarkers changes could be potentially useful to develop preventive measures before the onset of overt metabolic syndrome.

Collectively, these manuscripts confirm that sedentariety is harmful for the cardiovascular system. Moreover, exercise not only exerts positive effect on cardiovascular functions and reduces the risks of cardiovascular diseases (primary prevention), but could also revert cardiovascular disease and play a preventive role in the progression of pathological conditions (secondary/tertiary prevention).

Acknowledgments

The editors would like to thank the authors who have submitted their research to this special issue. The editors also acknowledge all reviewers for their contribution to this special issue. The lead guest editor thanks all guest editors for spending their precious time in handling the paper.

Antonio Crisafulli
Pasquale Pagliaro
Alain Cohen-Solal
Andrew J. Coats

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 165078, 11 pages
http://dx.doi.org/10.1155/2015/165078

Review Article

Effects of Physical (In)activity on Platelet Function

Stefan Heber and Ivo Volf

Institute of Physiology-Centre for Physiology & Pharmacology, Medical University of Vienna, Schwarzspanierstraße 17, 1090 Vienna, Austria

Correspondence should be addressed to Ivo Volf; ivo.volf@meduniwien.ac.at

Received 15 March 2015; Accepted 19 April 2015

Academic Editor: Pasquale Pagliaro

As platelet activation is closely related to the liberation of growth factors and inflammatory mediators, platelets play a central role in the development of CVD. Virtually all cardiovascular risk factors favor platelet hyperreactivity and, accordingly, also physical (in)activity affects platelet function. Within this paper, we will summarize and discuss the current knowledge on the impact of acute and habitual exercise on platelet function. Although there are apparent discrepancies regarding the reported effects of acute, strenuous exercise on platelet activation, a deeper analysis of the available literature reveals that the applied exercise intensity and the subjects' cardiorespiratory fitness represent critical determinants for the observed effects. Consideration of these factors leads to the summary that (i) acute, strenuous exercise can lead to platelet activation, (ii) regular physical activity and/or physical fitness diminish or prevent platelet activation in response to acute exercise, and (iii) habitual physical activity and/or physical fitness also favorably modulate platelet function at physical rest. Notably, these effects of exercise on platelet function show obvious similarities to the well-recognized relation between exercise and the risk for cardiovascular events where vigorous exercise transiently increases the risk for myocardial infarction and a physically active lifestyle dramatically reduces cardiovascular mortality.

1. Introduction

A large body of evidence indicates that both acute exercise and habitual physical activity affect platelet function. This is of special interest as the inflammatory and immunomodulatory consequences of platelet activation are increasingly recognized and platelets therefore seem to be of central importance not only to the final stages of cardiovascular disease (CVD), but also to the development of these diseases. Therefore, a modulation of platelet function by acute exercise and/or habitual physical activity might represent a mechanistic link between physical exertion and its observed effects on CVD. This would be especially interesting as a remarkable strong correlation exists between CVD-related mortality and physical activity, as we will discuss later in this review.

In order to give a structured overview based on currently available literature, the first part of this review will deal with the influence of acute (mostly strenuous) exercise on platelet function. To introduce the reader to different aspects of platelet activation as well as platelet function tests (and also as interpretation of obtained results may critically depend on the applied methodologies), this will be done from a platelet-centered view where different aspects of platelet activation are treated separately. Subsequently, the impact of exercise intensity and the subjects' cardiorespiratory fitness on the effects of exercise on platelet function is summarized and discussed, including the modulating effects of cardiorespiratory fitness/physical activity on platelet function in the resting state.

2. Introduction to Platelets and Their Function

Platelets represent the smallest formed elements of blood. They are anucleate cells with a life-span of 7–10 days and contain a variety of intracellular organelles, including different types of secretory granules.

Activation of platelets, finally resulting in platelet degranulation and aggregation, is essential for hemostasis and can be triggered by several specific platelet-stimulating mediators (e.g., thrombin, ADP, and elements of the extracellular matrix) as well as by shear and oxidative stress.

As blood platelets are of central importance to the process of (primary) hemostasis and coagulation, abnormalities in platelet function (resulting in thrombosis or bleeding) result in severe and potentially lethal consequences. In principle, activation of platelets immediately results in platelet aggregation and subsequent thrombus formation—however, these consequences of platelet activation can to some extent be antagonized by functional endothelium, pointing to a crucial role of endothelium-derived mediators that counteract platelet activation (namely, nitric oxide and prostacyclin) in this process. However, as activated platelets compromise endothelial function, the situation is complex.

The importance of platelets to the development of atherosclerotic disease is apparent from the fact that platelet activation is associated with accelerated atherosclerosis and correlates with severity of this disease in humans. An injection of activated platelets exacerbates the formation of native atherosclerotic lesions and an increase in systemic platelet activation has been described for a variety of atherosclerotic diseases including coronary artery disease [1, 2] and cerebrovascular disease [3].

While the in vitro assessment of platelet reactivity in different settings (including acute exercise and training) might include the final consequences of platelet activation (i.e., aggregation), measurement of in vivo platelet activation depends on more subtle parameters.

As different pathways of platelet activation might result in distinct patterns of "platelet activation markers," such studies require the consideration of several aspects of platelet activation for a final interpretation of obtained results.

3. Influence of Acute Exercise on Diverse Aspects of Platelet Activation

3.1. Platelet Count and Volume. Several studies show that acute exercise results in a transient increase in platelet count. This increase is caused by hemoconcentration and by platelet release from the liver, lungs, and, importantly, the spleen [4–6]. The latter contracts in response to elevated concentrations of epinephrine, as can be seen with increasing exercise intensity where epinephrine raises from preexercise plasma concentrations of 400–800 pM to >3500 pM with intense exercise [7–9]. Interestingly, platelets stored in the spleen have been reported to be significantly larger than normal circulating platelets [4, 6, 10]. Accordingly, some studies have reported an increase of mean platelet volume in response to exercise [11–13], although this could not be confirmed in all studies [14–16].

3.2. Activation of Glycoprotein IIb/IIIa. Glycoprotein IIb/IIIa (GPIIb/IIIa, integrin αIIbβ3) is constitutively expressed on the surface of resting platelets and represents the main fibrin(ogen) receptor on these cells. Upon platelet activation, this receptor undergoes a conformational change resulting in a drastically increased affinity towards fibrin(ogen), enabling the firm binding of platelets to fibrin(ogen) and thus facilitating platelet-platelet interaction, that is, platelet aggregation and the formation of stable thrombi. Only a limited number of studies found an increase in GPIIb/IIIa activation after exercise [11, 17]—most studies reported no such effects [13, 18–22].

3.3. Platelet Aggregation. Potential effects of exercise on platelet aggregation have been addressed by a multitude of studies using different techniques. The vast majority of these studies found increased platelet aggregability after exercise in response to various agonists, while a few studies found no such effect [23–26] or even an inhibition of platelet aggregation by exercise [16, 27, 28]. Importantly, platelet aggregation is affected by cell density (see above); therefore, interpretation of experimental results might be difficult, as an increase in agonist-induced platelet aggregation is not necessarily related to platelet hyperreactivity when platelet count is not corrected.

Nevertheless, increased platelet aggregation in response to exercise was observed by light transmission aggregometry without [11, 15, 29–32] and after adjustment of platelet count in platelet-rich plasma (PRP) [21, 33, 34], but also with other techniques including electrical impedance aggregometry [13, 35–41], filtragometry [42–44], calculation of reduction of single (unaggregated) platelets after agonist stimulation [45–50], and platelet aggregation after application of shear stress by a rotational viscometer [20, 51, 52]. Notably, this observed increase of in vitro platelet aggregation after acute exercise is not in contrast to those studies that found no effects of exercise on GPIIb/IIIa activation, as platelet aggregation rather depends on sensitivity of platelets towards agonists than on the basal activation state of glycoprotein IIb/IIIa.

Another test indicative of platelet aggregate formation (following adhesion at high shear) is carried out by the Platelet Function Analyzer (PFA-100), where platelets in whole blood are activated by the combined action of shear stress and agonists, resulting in closure of an aperture. After exercise, shorter closure times have been reported [26, 29, 53]; however, also these results have to be interpreted in light of the fact that this assay can be influenced by platelet count [54], which was increased in two of these three studies after exercise; in the third study [29] no data regarding platelet count have been provided. Decreased closure times in response to exercise were also observed with hemostatometry [55, 56], where defined pressure is applied to drive blood flow through tubing and time until closure due to platelet plug formation is measured after puncture of the tubing.

3.4. Platelet Adhesion. Various platelet adhesion assays have been used in the literature to test for an effect of exercise on platelet function. These studies have yielded inconsistent results; whereas one study showed decreased platelet adhesion to fibrinogen (evoked by shear-stress with a rotational viscometer) [20], other groups (using different experimental techniques) did not find any effect [23, 32, 58]; however, results of one study [57] indicate a role of exercise intensity-dependent cortisol levels in this process. Wang et al. used an assay which was designed to test the resistance of adhered platelets against detachment by defined shear stress applied by a flow of buffer. With this method, the authors found more adhering platelets after exhaustive

exercise [45, 47–49, 59], indicative of a stronger platelet-surface interaction in response to acute exercise.

3.5. Platelet Degranulation. Degranulation represents an integral consequence of platelet activation that results in the concomitant release of a variety of soluble mediators and the expression of distinct proteins on the platelet surface due to membrane fusion of the granules with the platelet membrane. Consequently, de novo protein expression, for example, of P-selectin (CD62P), on the platelet plasma membrane as well as plasma levels of soluble mediators, for example, β-thromboglobulin (β-TG, CXCL7) and platelet factor 4 (PF4, CXCL4), can be used as a measure of (in vivo) platelet degranulation/activation.

After exercise, several studies found increased plasma levels of β-thromboglobulin [30, 31, 37, 45, 60, 61] and platelet factor 4 [27, 45, 60, 62]. As both β-thromboglobulin and platelet factor 4 represent very sensitive marker of platelet activation, these findings represent strong evidence that exercise activates platelets, although a small number of studies reported unchanged [26, 63] or decreased [16] levels of β-thromboglobulin after exercise.

Although the (activation-dependent) expression of P-selectin is not restricted to platelets, the fact that degranulation initially results in the expression of membrane-bound P-selectin (that is later on cleaved off to form soluble P-selectin) makes this glycoprotein an invaluable marker of platelet activation. P-Selectin represents a pivotal adhesion molecule mediating cell-cell contact of platelets with leukocytes, endothelial cells, and other platelets. Binding of platelet P-selectin to its receptor PSGL-1 on leukocytes results in aggregate formation of platelets with leukocytes (see below), promoting the stimulation of leukocytes—a process involved in many inflammatory conditions.

The influence of acute exercise on the expression of P-selectin on platelets has been addressed by several studies and yielded contradictory results. Basal P-selectin expression (i.e., without intentional platelet stimulation applied ex vivo) has been found to be increased [17, 42, 44, 64–68] after acute exercise, although this was not in all studies statistically significant [13, 18, 21]. Notably, several studies found no influence of exercise on basal P-selectin expression [11, 19, 22, 69–71]. Agonist (including shear stress) induced P-selectin expression after exercise was increased in most studies [17, 42, 44, 51, 66, 69, 70]; but again this effect was not always significant [18], absent [19, 22, 71] or there was even a decrease in P-selectin [20]. Similarly, soluble P-selectin was shown to be increased [21, 49, 72] or unchanged [20, 51, 73] after exercise.

3.6. Platelet-Leukocyte Aggregates. Consistent with results of studies showing increased platelet P-selectin expression after exercise, formation of aggregates with (various subsets of) leukocytes (platelet-leukocyte aggregates, PLAs) has been detected in response to acute exercise.

Overall PLAs were found to be increased [42, 69] and studies specifically addressing the involved leukocyte subtypes found increased numbers of platelet-granulocyte aggregates [70, 71], including platelet-neutrophil [16, 22, 44] and -eosinophil aggregates [22] and also platelet-lymphocyte [70] and -monocyte aggregates [44, 67, 70, 71]. Only one single study reported a reduction of platelet-monocyte aggregates after exercise [74].

Within these studies, both basal [16, 42, 44, 67, 69–71, 74] and agonist-induced [22, 42, 44, 69–71] formation of platelet-leukocyte aggregates were determined.

3.7. Platelet-Derived Microparticles. A further possible consequence of platelet activation is the release of platelet-derived microparticles (PDMPs) that constitute small (between 0.1 μm and 1.0 μm) membrane vesicles that represent an important link between platelet activation and plasmatic coagulation, as PDMPs provide a large surface of phosphatidylserine necessary for tenase and prothrombinase complex formation. After exercise, the levels of PDMPs in plasma have been reported to be increased [75–77], although some studies could confirm this finding only in response to platelet agonists [70] or to the application of shear stress [78, 79].

3.8. Thromboxane A_2. Platelet activation also involves the release of effectors that are part of positive feedback loops for platelet activation in an auto- and paracrine manner. Besides ADP, a molecule of pivotal importance in this context is thromboxane A_2, which is synthesized upon platelet activation. Its degradation product thromboxane B_2 serves as a marker of in vivo platelet activation that can be readily measured. After exercise, elevated plasma [25, 32, 35–37, 42, 66] as well as urinary levels [11, 50] of thromboxane B_2 have been detected, consistent with a platelet-activating effect of acute exercise.

3.9. Platelet Cytosolic Calcium. Modulation of the concentration of cytosolic Ca^{2+} represents a mechanism of central importance to the activation state of platelets. Increased cytosolic free calcium ions constitute a very early event of platelet activation and function as important second messengers in platelets. An increase in cytosolic Ca^{2+} has consistently been reported after exercise [34, 46, 48, 59, 80], although some authors only reported small, nonsignificant effects [38, 50]. Additionally, also agonist-induced Ca^{2+} levels have been found to be increased after exercise [46, 48, 59, 80].

3.10. Platelet Inhibiting Pathways. Nitric oxide (NO), prostacyclin (PGI_2), and CD39/CD73 represent the physiologic effectors of the three major pathways that are relevant to the inhibition of platelet function (for a detailed review see [81]).

(Increased) production and release of both NO and prostacyclin is mediated by an increase in cytosolic calcium concentration, which can be triggered by shear stress (what is obviously relevant to exercise) and a multitude of other mediators. Whereas NO is produced by platelets as well as other cells including endothelial cells and red blood cells, prostacyclin synthesis occurs in endothelial cells and smooth muscle cells but is absent in platelets. Redundancy between these two systems has been reported, where one system takes over when the other one is compromised, for example, increased NO generation when prostacyclin production is

impaired [82]. Both NO and PGI_2 inhibit platelet function via an increase of cyclic nucleotides (NO mainly via cGMP and prostacyclin via cAMP), which subsequently activate their respective protein kinases (cGMP: protein kinase G; cAMP: protein kinase A), which in turn phosphorylate key proteins ultimately leading to platelet inhibition. Notably, since platelet activation is associated with an increase in cytosolic calcium concentration, NO generation within platelets represents also an early consequence of platelet activation, thereby playing an important autoregulatory role that limits excessive aggregation, adhesion, and thrombus growth [83, 84]. Thus, increased intraplatelet amounts of cyclic nucleotides can be the result of (and indicative of) platelet inhibition, for example, by the endothelium (release of NO and PGI_2), or also a result of platelet activation. Consequently, direct and indirect quantification of NO and PGI_2 may provide information concerning the production of these compounds but do not necessarily indicate inhibition of platelets as the net effect of activating versus inhibitory stimuli remains obscure without a direct assessment of platelet function.

Due to their short in vivo half-life, both NO and PGI_2 are commonly quantified by their degradation products nitrite and nitrate (in the case of NO) and 6-keto-$PGF_{1\alpha}$ (in the case of prostacyclin).

Available studies indicate increased prostacyclin generation in response to acute exercise [32, 37, 49, 66, 85–88] and increased intraplatelet levels of cAMP [66, 80] indicate that platelets are indeed affected.

Similarly, increased plasma levels of NO degradation products nitrite and nitrate have been observed together with platelet activation [34, 46, 48, 50, 80, 85] after acute exercise. While also red blood cells represent a possible source for NO production in response to exercise [89], the functional relevance of increased levels of NO degradation products critically depends on the bioavailability of nitric oxide. As increased generation of NO might be counterbalanced by its inactivation, for example, by reactive oxygen species, observed levels of NO metabolites do not always indicate biologically active NO. However, increased cGMP levels within platelets [48, 66, 80] (in part accompanied by increased platelet aggregability in response to collagen [38]) have been detected in response to exercise, which strongly argue for an increased bioavailability of NO. Notably, one study also reported unchanged basal but decreased cGMP levels in response to the NO-donor SIN-1 [33] after exercise, which would indicate decreased platelet sensitivity towards NO.

CD39/CD73 constitutes a further pathway that interferes with platelet function. CD39 is expressed on a number of vascular cells, including endothelial cells and platelets [90, 91]. CD39 cleaves ADP and ATP to AMP, consequently limiting platelet activation via P2-receptors. AMP is further broken down by endothelial CD73 to adenosine [92], which inhibits platelets via interaction with their A_2-receptors and a subsequent increase in cAMP. After exercise, basal as well as ADP-induced CD39 expression on platelets has been reported to be decreased while ADP-stimulation increased CD39-expression before as well as after exercise [21]. This is contrastive to other aspects of platelet function (e.g., expression of P-selectin), where agonists and exercise alter platelet function in a similar manner. Thus, the observed exercise-induced decrease in CD39 expression should be interpreted to represent a mechanism facilitating platelet activation rather than a consequence of platelet activation.

Short Summary. Taken together, despite some inconsistency and contradictory results, the majority of available studies indicate that acute exercise exerts a significant influence on virtually all aspects of platelet activation. Although (also) different protocols might partly account for contradictory results found in the literature, results from several studies indicate that the applied exercise intensity might represent a critical determinant for the platelet-activating effects of acute exercise.

4. Exercise Intensity and Platelet Function

To test for the hypothesis that exercise intensity affects platelet function, one has to consider that there are several ways to define exercise intensity—each with certain advantages and drawbacks. Although it is beyond the scope of this review to discuss this topic in detail (for a comprehensive overview of different methods to determine and to prescribe exercise intensity the reader is referred to a recent review by Mann et al. [93]), one critical issue has to be mentioned. Most studies dealing with acute exercise and platelet function that are covered within this review defined (or prescribed) exercise intensity as a percentage of maximal oxygen consumption, indeed a very well accepted and widely used strategy. Nevertheless, it is well established that a given percentage of maximal oxygen consumption can result in great interindividual differences in metabolic stress, for example, catecholamine levels and blood pH, which are most likely to influence platelet function during physical exercise. Thus, a comparison of results obtained from different studies is compromised by these limitations.

Nevertheless, a few studies directly compared different exercise intensities with regard to their effects on platelets. These studies provide substantial evidence that exercise intensity indeed represents a critical determinant of platelet activation. Wang et al. [45] compared an incremental exercise test until exhaustion with 30 minutes of continuous exercise at 50–55% of maximal oxygen consumption (VO_2max). Whereas the 30-minute submaximal trial resulted in decreased platelet adhesion and aggregation (β-TG and PF4 remained unchanged), all of these parameters were increased after the incremental test until exhaustion. These results were basically confirmed by a study with similar study design [80], where also cytosolic Ca^{2+} levels were measured. Intraplatelet Ca^{2+}—basal as well as after ADP stimulation—was shown to be increased only after the incremental test. Similarly, Chicharro et al. [15] reported that platelet aggregation was unchanged after low intensity running for 30 minutes without an increase in blood lactate levels, whereas running for the same duration leading to a mean lactate concentration of 4.6 mmol/L (at rest: mean 0.9 mmol/L) resulted in significantly increased aggregation in response to ADP. These results are in line with results from another group that found increased aggregability in response

to ADP and collagen after an incremental exercise test (bicycle ergometer) until exhaustion, whereas aggregability was largely unchanged after 30 minutes of cycling with an intensity of 60% VO_2max and even decreased in response to low concentrations of platelet agonist [34]. Cadroy et al. [26] applied 30 minutes of cycling to compare two relatively moderate intensities (50% versus 70% VO_2max) with respect to their effects on platelet function. These authors did not observe any effects on platelet aggregation but found reduced closure time measured with the PFA-100 in response to epinephrine and ADP. Notably, these effects were more pronounced at the higher intensity. Comparable intensities (corresponding to about 55% and 80% of VO_2max, resp.) were applied in a study where intensities were defined by means of 90% or 130% of the first ventilatory threshold (an intensity above which lactate accumulation in plasma occurs, but a steady state is still reached during continuous exercise). In this study, hemostatometry readings in terms of increased thrombus formation were only affected by the higher intensity [56].

More recent studies also addressed P-selectin expression and platelet-leukocyte formation. Wang et al. [22] observed more PLAs in response to shear stress, LPS and fMLP after 40 minutes of cycling at 80% of VO_2max compared to rest, but less PLAs (compared to rest) in response to an exercise intensity of 40% VO_2max. Notably, there were no stimulatory effects of exercise on PLAs in the absence of agonists. Also Hilberg et al. analyzed P-selectin expression as well as different subsets of PLAs in a study where they compared effects of an incremental step test until exhaustion with those of 45 minutes at 90% of the IAT (individual anaerobic threshold, a threshold concept taking into account the rate of decrease of lactate concentration after the end of an incremental exercise test) [71]. Whereas the amount of PLAs—both basal and after platelet activation by TRAP-6—was increased after both exercise interventions, basal P-selectin expression remained unaffected. However, the incremental exercise test resulted in increased agonist-stimulated P-selectin expression. In a subsequent study, the same authors accounted for the potential confounding effects of different exercise durations between groups (as is the case when comparing, i.e., an incremental test of 10–15 min and a submaximal test of 60 min duration) and applied 45–60 minutes of cycling to compare intensities of 80% and 100% of the IAT with respect to their effects on platelet function. Again, they found increased agonist-stimulated P-selectin expression—albeit no difference between exercise intensities—but also increased formation of platelet leukocyte aggregates, which was significantly more pronounced in response to the higher exercise intensity.

Experiments performed with an ergometer for the upper limbs [35] indicate that a interrelation between exercise intensity and platelet activation is not specific for running or cycling. While TXB_2 was increased after an incremental exercise test until exhaustion but not after 15 minutes of continuous exercise at 75% of maximal heart rate, platelet aggregation increased in response to both exercise protocols, but this increase was more marked after the incremental test.

5. Influence of Cardiorespiratory Fitness on Platelet Function

Besides exercise intensity, also cardiorespiratory fitness, that is, the adaptation to long-term exercise training, might represent a critical determinant for alterations of platelet function in response to acute exercise.

Some studies directly compared the effects of acute, strenuous exercise on platelet function between two groups differing in cardiorespiratory fitness and habitual physical activity, respectively. By and large, results obtained from these studies suggest that low cardiorespiratory fitness results in greater platelet activation after acute exercise. Kestin et al. [18] compared the effects of an incremental exercise test on the expression of several receptors located on the platelet surface between sedentary and physically active healthy volunteers. In sedentary individuals, surface expression of GPIb was downregulated (as is the case after stimulation with thrombin [94, 95]), while CD36 was upregulated (consistent with platelet activation [96]) and the fibrinogen receptor GPIIb/IIIa was significantly more activated (in response to thrombin) after exercise. In contrast, none of these changes could be observed in the fitter volunteers. Consistent with these results, platelets of sedentary volunteers showed higher aggregability and adhesiveness after an incremental exercise test performed on a bicycle ergometer compared with platelets of (significantly, but not much fitter) physically active volunteers [45]. Additionally, the increase of plasma β-TG and PF4 tended to be more pronounced in the sedentary group. Coppola et al. [21] also compared sedentary with active subjects and found a significantly elevated number of circulating platelet-platelet aggregates after an incremental exercise test in both groups—however, levels were much higher in sedentary volunteers. Moreover, ADP-stimulated P-selectin expression as well as platelet aggregation was only increased in sedentary volunteers after exercise.

Another recently published study assessed the effect of acute (moderate) exercise on the occurrence and procoagulant activity of platelet-derived microparticles. In untrained as well as highly trained individuals, 90 minutes of cycling at 80% of IAT caused a significant increase in both the number of PDMPs and their coagulant activity. However, after two hours the number of PDMPs remained significantly elevated only in untrained subjects [76]. Such a difference in the amounts of highly coagulant microparticles between sedentary and highly trained subjects in the postexercise phase represents an interesting finding, as there is increased risk for sudden cardiac death within this period and this risk is substantially greater for sedentary individuals [97]. Additionally, it should be mentioned that the chosen exercise intensity of 80% of IAT corresponded to 60% of maximal power output (reached in an incremental test) in trained subjects but only to 45% of maximal power output in sedentary individuals. Consequently, trained subjects performed exercise at a higher percentage of their VO_2max and their platelets were exposed to a higher shear stress. This is especially relevant in light of the fact that shear stress is able

to activate platelets and therefore should be considered when interpreting the results of this study.

In addition, also longitudinal studies have been carried out, where acute effects of exercise on platelet function were assessed before and after a long-term exercise training program. In an early study including only 6 healthy volunteers, 20 minutes of cycling with 70–80% of maximal heart rate was shown to cause a significantly increased slope of ADP-induced platelet aggregation, while 12 weeks of regular exercise training abrogated this response to acute exercise. In line with these findings, Wang et al. [47, 48] observed increased platelet aggregability and adhesiveness in response to an incremental exercise test until exhaustion and this effect was diminished or absent after 8 weeks of regular training. Similarly, the exercise-related increase in intraplatelet calcium was blunted after the training period [48]. Subsequent studies by the same authors confirmed these results also for platelet activation by shear stress [51] and oxidized LDL [46]. Notably, all these effects were reversible after several weeks of detraining.

In a population predestined to be particularly unfit, namely, (untrained) patients with spinal cord injury, El-Sayed et al. [98] observed increased aggregation in response to ADP and collagen after 30 minutes of arm cranking exercise with an intensity as little as 60–65% of peak oxygen consumption. However, after 12 weeks of regular exercise training, acute exercise had the opposite effect, namely, an inhibition of aggregation. Furthermore, Chen et al. [79] recently observed an increase of shear-induced PDMP-formation after an incremental exercise test in sedentary volunteers, an effect that was absent after 4 weeks of regular exercise training.

Taken together, these studies show that regular exercise training mitigates the activating effect of acute, strenuous exercise on platelet function. In addition, a number of studies indicate that long-term exercise training also affects platelet function at rest.

An early study performed in overweight, hypertensive men showed that low intensity training (walking/slow jogging exercise at 45–55% VO_2max, 5x/week for 45–60 min) for 12 weeks led to a reduction of secondary platelet aggregation in blood that was sampled at physical rest [99]. These findings were confirmed and extended by another study also performed in hypertensive patients by de Meirelles et al. [100], who demonstrated decreased platelet aggregation in response to collagen after a period of regular exercise training (12 weeks, 75–85% of maximal heart rate, 3x/week for 40 min). These effects might be attributed to increased levels of nitric oxide, as L-arginine uptake into platelets, NOS-activity, and cGMP levels were increased after the training period.

Importantly, effects of exercise training on basal platelet function have also been shown in healthy volunteers. Exercise training performed on a bicycle ergometer 5x/week for 30 min over a period of ~8 weeks with healthy, but (initially) sedentary, men or women, respectively (at 60% or 50% VO_2max), decreased both platelet adhesion and aggregation in response to several stimuli, including oxidized LDL and shear stress [46–48, 51]. Additionally, training decreased intracellular calcium levels and increased cGMP levels within platelets as well as increased NO-metabolites in plasma [48]. Indications that exercise training modulates platelet function via the nitric oxide pathway were also obtained from a study in young, sedentary male volunteers where 20 weeks of ergometer training (60% VO_2max, 3x/week for 30 min) increased plasma and intraplatelet nitrite/nitrate levels and decreased platelet aggregation in response to collagen and ADP [101]. However, a study performed with 7 spinal cord injury patients was not able to show an effect of arm crank exercise (12 weeks, 60–65% VO_2max 3x/week for 30 min) on platelet aggregation at rest [98].

Taken together, the majority of available studies conclude that exercise training affects basal platelet function in an antithrombotic manner. Studies performed with patients suffering from peripheral arterial disease indicate that effects on platelet function are apparent after a remarkable short duration of exercise training as 2 training weeks (strength training, 30 min effort-free cycle ergometer, 30 min treadmill walking at 3.2 km/h daily) was sufficient to decrease platelet adhesion to fibrinogen (while showing no effect on platelet aggregation) [102]. In healthy volunteers, no short-term training studies have been performed but it is evident that low intensity training is sufficient to affect platelet function in a favorable way. While only limited data are available on the effects of high volume and/or high intensity training on platelet function, there are indications that basal platelet function might be hyperresponsive in competitive athletes (male cyclists) compared to sedentary controls [103]. Nevertheless, these data have only been obtained with the PFA-100 and therefore might have been affected by the different hematologic profile of professional athletes (i.e., hematocrit), so additional studies are clearly required to address this important point.

In any way, physical activity habits and cardiorespiratory fitness appear to have major impact on platelet reactivity, but it should be kept in mind that platelet function observed in physically active subjects obviously represents the physiologic state; therefore, the conclusion that a sedentary lifestyle and low cardiorespiratory fitness affects platelet function in a prothrombotic, proinflammatory manner would probably describe this issue in an accurate way.

Considering exercise intensity as well as physical activity and fitness, inconsistencies between different studies cited in the first, platelet function centered part of this review can be partly explained. For example, in those studies reporting inhibition of platelet aggregation [16, 27, 28] in response to acute exercise, submaximal, prolonged exercise protocols were applied in trained individuals, whereas the majority of studies reporting increased aggregability prescribed maximal exercise protocols until exhaustion to untrained individuals. Further, a relatively moderate exercise protocol (30 min, 60% VO_2max) was used in the cited study reporting a decrease in platelet adhesion in response to exercise [20]. Moreover, in contrast to those studies where increased β-TG plasma levels were measured after exhaustive exercise, unchanged or decreased levels were only observed after 20–30 min exercise protocols with an intensity not higher than 70% of VO_2max or maximal heart rate, respectively [16, 26].

6. Summary and Conclusion

Available literature that has been summarized in this review indicates that (i) acute, strenuous exercise can lead to platelet activation, (ii) regular physical activity and/or physical fitness prevent platelet activation in response to acute exercise, at least to a certain degree, and (iii) although a remarkable low number of studies have been performed on this topic in healthy populations, habitual physical activity and/or physical fitness also favorably modulate platelet function at physical rest.

Therefore, physical activity habits and cardiorespiratory fitness appear to have major impact on platelet reactivity, but it should be kept in mind that platelet function observed in physically active subjects obviously represents the physiologic state, since endurance exercise—especially running—played a key role in the evolution of the human species [104]. Therefore, the conclusion that a sedentary lifestyle and low cardiorespiratory fitness affects platelet function in a prothrombotic manner would probably describe this issue in an accurate way and this viewpoint is also supported from studies where the training phase was followed by a period of deconditioning.

Obviously, platelet function is directly and indirectly affected by physical (in)activity. In this regard, several mechanisms and cell/tissue types are supposed to contribute to the observed effects. Acute exercise results in increased levels of catecholamines as well as increased shear and oxidative stress, all of which are known to activate platelets. This is especially relevant as artery blood flow and shear rate increase in parallel to exercise intensity [105]. While enhanced shear tends to activate platelets, it also stimulates the endothelial production of nitric oxide. Endothelial nitric oxide affects bypassing platelets (thereby counteracting their activation) as well as vascular smooth muscle cells in the medial layer of the artery. The latter results in vessel dilation and, consequently, increased blood flow at lower shear.

As both NO production and antioxidant defense are increased as a consequence of training, also bioavailability of NO is affected by regular exercise and this would help to explain several effects of physical (in)activity on platelet function even more as low shear rates have been shown to stimulate endothelial ROS generation [106].

Notably, while short-term exercise training enhances production and bioavailability of NO, long-term adaptations taking place in specific vascular regions induce structural changes to the vessel resulting in an increase in lumen diameter, thereby decreasing shear rates while normalizing endothelial NO production [107, 108]. Interestingly, there is evidence that also extreme levels of activity might result in detrimental effects to the cardiovascular system [109], but it is unclear at the moment if this also holds true for platelet function.

While the contribution of platelets to the final stages of CVD is obvious, the central importance of these cells and their activation state to the development of cardiovascular disease is increasingly appreciated as chronic platelet activation and platelet hypersensitivity result in increased liberation of growth factors and proinflammatory mediators. Therefore, it is of special interest that the effects of (both acute and chronic) exercise on platelet function show obvious similarities to outcomes from epidemiologic studies on the impact of exercise on the development of cardiovascular events where it has been shown that vigorous exercise transiently increases the risk for myocardial infarction [110–112]. Approximately 6 to 17 percent of sudden deaths have been shown to occur in association with physical exertion [97] and this risk is considerably lower in populations that perform exercise on a regular base [113]. Further, several studies were able to show a strong, inverse, and independent association between cardiorespiratory fitness and cardiovascular (as well as overall) mortality risk [114–116].

This obvious parallelism poses the intriguing question if the assessment of platelet function in response to acute and habitual exercise might help to predict the beneficial effects of physical activity/fitness on (the development of) CVD. This would offer the possibility of acquiring information from platelet-related studies that is not available from long-term studies with cardiovascular events defined as the primary endpoint. Consequently, this would also allow directly studying and comparing the potential effectivity of different training programs and exercise intensities for primary and secondary prevention of CVD. Although this is speculative at the moment, clearly more research is required on this highly relevant topic as well as on the mechanisms that are involved in the modulation of platelet function by habitual exercise.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] M. Gawaz, F.-J. Neumann, I. Ott, A. Schiessler, and A. Schömig, "Platelet function in acute myocardial infarction treated with direct angioplasty," *Circulation*, vol. 93, no. 2, pp. 229–237, 1996.

[2] I. Ott, F.-J. Neumann, M. Gawaz, M. Schmitt, and A. Schömig, "Increased neutrophil-platelet adhesion in patients with unstable angina," *Circulation*, vol. 94, no. 6, pp. 1239–1246, 1996.

[3] N. M. Smith, R. Pathansali, and P. M. W. Bath, "Platelets and stroke," *Vascular Medicine*, vol. 4, no. 3, pp. 165–172, 1999.

[4] K. G. Chamberlain, M. Tong, and D. G. Penington, "Properties of the exchangeable splenic platelets released into the circulation during exercise-induced thrombocytosis," *American Journal of Hematology*, vol. 34, no. 3, pp. 161–168, 1990.

[5] K. G. Schmidt and J. W. Rasmussen, "Exercise-induced changes in the in vivo distribution of ^{111}In-labelled platelets," *Scandinavian Journal of Haematology*, vol. 32, no. 2, pp. 159–166, 1984.

[6] D. Bakovic, N. Pivac, D. Eterovic et al., "The effects of low-dose epinephrine infusion on spleen size, central and hepatic circulation and circulating platelets," *Clinical Physiology and Functional Imaging*, vol. 33, no. 1, pp. 30–37, 2013.

[7] S. R. Bird, M. Linden, and J. A. Hawley, "Acute changes to biomarkers as a consequence of prolonged strenuous running," *Annals of Clinical Biochemistry*, vol. 51, no. 2, pp. 137–150, 2014.

[8] F. O. Pires, T. D. Noakes, A. E. Lima-Silva et al., "Cardiopulmonary, blood metabolite and rating of perceived exertion

responses to constant exercises performed at different intensities until exhaustion," *British Journal of Sports Medicine*, vol. 45, no. 14, pp. 1119–1125, 2011.

[9] H. Zouhal, C. Jacob, P. Delamarche, and A. Gratas-Delamarche, "Catecholamines and the effects of exercise, training and gender," *Sports Medicine*, vol. 38, no. 5, pp. 401–423, 2008.

[10] D. Bakovic, N. Pivac, D. Eterovic et al., "Changes in platelet size and spleen volume in response to selective and non-selective β-adrenoceptor blockade in hypertensive patients," *Clinical and Experimental Pharmacology and Physiology*, vol. 36, no. 4, pp. 441–446, 2009.

[11] J. P. Whittaker, M. D. Linden, and V. G. Coffey, "Effect of aerobic interval training and caffeine on blood platelet function," *Medicine & Science in Sports & Exercise*, vol. 45, no. 2, pp. 342–350, 2013.

[12] G. Lippi, G. L. Salvagno, E. Danese, C. Tarperi, G. C. Guidi, and F. Schena, "Variation of red blood cell distribution width and mean platelet volume after moderate endurance exercise," *Advances in Hematology*, vol. 2014, Article ID 192173, 4 pages, 2014.

[13] F. A. J. L. Scheer, A. D. Michelson, A. L. Frelinger III et al., "The human endogenous circadian system causes greatest platelet activation during the biological morning independent of behaviors," *PLoS ONE*, vol. 6, no. 9, Article ID e24549, 2011.

[14] A. Kratz, M. J. Wood, A. J. Siegel, J. R. Hiers, and E. M. van Cott, "Effects of marathon running on platelet activation markers: direct evidence for in vivo platelet activation," *American Journal of Clinical Pathology*, vol. 125, no. 2, pp. 296–300, 2006.

[15] J. L. Chicharro, O. Sänchez, F. Bandrés et al., "Platelet aggregability in relation to the anaerobic threshold," *Thrombosis Research*, vol. 75, no. 3, pp. 251–257, 1994.

[16] H. Aldemir and N. Kiliç, "The effect of time of day and exercise on platelet functions and platelet-neutrophil aggregates in healthy male subjects," *Molecular and Cellular Biochemistry*, vol. 280, no. 1-2, pp. 119–124, 2005.

[17] E. E. Peat, M. Dawson, A. Mckenzie, and W. S. Hillis, "The effects of acute dynamic exercise on haemostasis in first class Scottish football referees," *British Journal of Sports Medicine*, vol. 44, no. 8, pp. 573–578, 2010.

[18] A. S. Kestin, P. A. Ellis, M. R. Barnard, A. Errichetti, B. A. Rosner, and A. D. Michelson, "Effect of strenuous exercise on platelet activation state and reactivity," *Circulation*, vol. 88, no. 4, pp. 1502–1511, 1993.

[19] S. Lindemann, B. Klingel, A. Fisch, J. Meyer, and H. Darius, "Increased platelet sensitivity toward platelet inhibitors during physical exercise in patients with coronary artery disease," *Thrombosis Research*, vol. 93, no. 2, pp. 51–59, 1999.

[20] J.-S. Wang and C.-H. Liao, "Moderate-intensity exercise suppresses platelet activation and polymorphonuclear leukocyte interaction with surface-adherent platelets under shear flow in men," *Thrombosis and Haemostasis*, vol. 91, no. 3, pp. 587–594, 2004.

[21] A. Coppola, L. Coppola, L. dalla Mora et al., "Vigorous exercise acutely changes platelet and B-lymphocyte CD39 expression," *Journal of Applied Physiology*, vol. 98, no. 4, pp. 1414–1419, 2005.

[22] J.-S. Wang, H.-L. Yen, and C.-M. Yang, "Warm-up exercise suppresses platelet-eosinophil/neutrophil aggregation and platelet-promoted release of eosinophil/neutrophil oxidant products enhanced by severe exercise in men," *Thrombosis and Haemostasis*, vol. 95, no. 3, pp. 490–498, 2006.

[23] M. Lamprecht, H. Moussalli, G. Ledinski et al., "Effects of a single bout of walking exercise on blood coagulation parameters in obese women," *Journal of Applied Physiology*, vol. 115, no. 1, pp. 57–63, 2013.

[24] W. Siess, R. Lorenz, P. Roth, and P. C. Weber, "Plasma catecholamines, platelet aggregation and associated thromboxane formation after physical exercise, smoking or norepinephrine infusion," *Circulation*, vol. 66, no. 1, pp. 44–48, 1982.

[25] Y. Kishi, T. Ashikaga, and F. Numano, "Inhibition of platelet aggregation by prostacyclin is attenuated after exercise in patients with angina pectoris," *American Heart Journal*, vol. 123, no. 2, pp. 291–297, 1992.

[26] Y. Cadroy, F. Pillard, K. S. Sakariassen, C. Thalamas, B. Boneu, and D. Riviere, "Strenuous but not moderate exercise increases the thrombotic tendency in healthy sedentary male volunteers," *Journal of Applied Physiology*, vol. 93, no. 3, pp. 829–833, 2002.

[27] J. B. Knudsen, U. Brodthagen, J. Gormsen, R. Jordal, K. Nørregaard-Hansen, and P. E. Paulev, "Platelet function and fibrinolytic activity following distance running," *Scandinavian Journal of Haematology*, vol. 29, no. 5, pp. 425–430, 1982.

[28] M. S. El-Sayed, "Effects of alcohol ingestion post-exercise on platelet aggregation," *Thrombosis Research*, vol. 105, no. 2, pp. 147–151, 2002.

[29] E. H. Madsen, M. K. Christiansen, E. B. Schmidt, T. S. Poulsen, and S. R. Kristensen, "Effect of exercise on platelet activation during aspirin or clopidogrel intake in healthy men," *Platelets*, vol. 20, no. 3, pp. 177–182, 2009.

[30] H. Furui, N. Taniguchi, K. Yamauchi, I. Sotobata, H. Saito, and H. Inagaki, "Effects of treadmill exercise on platelet function, blood coagulability and fibrinolytic activity in patients with atrial fibrillation," *Japanese Heart Journal*, vol. 28, no. 2, pp. 177–184, 1987.

[31] S. Ahmadizad and M. S. El-Sayed, "The effects of graded resistance exercise on platelet aggregation and activation," *Medicine & Science in Sports & Exercise*, vol. 35, no. 6, pp. 1026–1032, 2003.

[32] D. Feng, J. Murillo, P. Jadhav et al., "Upright posture and maximal exercise increase platelet aggregability and prostacyclin production in healthy male subjects," *British Journal of Sports Medicine*, vol. 33, no. 6, pp. 401–404, 1999.

[33] S.-Y. Sakita, Y. Kishi, and F. Numano, "Acute vigorous exercise attenuates sensitivity of platelets to nitric oxide," *Thrombosis Research*, vol. 87, no. 5, pp. 461–471, 1997.

[34] M. G. Tozzi-Ciancarelli, M. Penco, and C. Di Massimo, "Influence of acute exercise on human platelet responsiveness: possible involvement of exercise-induced oxidative stress," *European Journal of Applied Physiology*, vol. 86, no. 3, pp. 266–272, 2002.

[35] G. Ersöz, A. M. Zergeroğlu, H. Fıçıcılar et al., "Effect of submaximal and incremental upper extremity exercise on platelet function and the role of blood shear stress," *Thrombosis Research*, vol. 108, no. 5-6, pp. 297–301, 2002.

[36] G. Ersöz, A. M. Zergeroğlu, and A. Yakaryılmaz, "The effect of submaximal exercise on platelet aggregation during late follicular and midluteal phases in women," *Thrombosis Research*, vol. 108, no. 2-3, pp. 147–150, 2002.

[37] H.-C. Hsu, Y.-T. Lee, and M.-F. Chen, "Exercise shifts the platelet aggregation modulatory role from native to mildly oxidized low-density lipoprotein," *Medicine and Science in Sports and Exercise*, vol. 32, no. 5, pp. 933–939, 2000.

[38] N. Kasuya, Y. Kishi, S.-Y. Sakita, F. Numano, and M. Isobe, "Acute vigorous exercise primes enhanced NO release in human platelets," *Atherosclerosis*, vol. 161, no. 1, pp. 225–232, 2002.

[39] L. Vucinic, I. Singh, F. J. Spargo, J. A. Hawley, and M. D. Linden, "Gamma tocopherol supplementation prevents exercise induced coagulation and platelet aggregation," *Thrombosis Research*, vol. 125, no. 2, pp. 196–199, 2010.

[40] H. Ficicilar, A. M. Zergeroglu, D. Tekin, and G. Ersoz, "The effects of acute exercise on plasma antioxidant status and platelet response," *Thrombosis Research*, vol. 111, no. 4-5, pp. 267–271, 2003.

[41] A. A. Hanke, A. Staib, K. Görlinger, M. Perrey, D. Dirkmann, and P. Kienbaum, "Whole blood coagulation and platelet activation in the athlete: a comparison of marathon, triathlon and long distance cycling," *European Journal of Medical Research*, vol. 15, no. 2, pp. 59–65, 2010.

[42] C. Perneby, N. H. Wallén, H. Hu, N. Li, and P. Hjemdahl, "Prothrombotic responses to exercise are little influenced by clopidogrel treatment," *Thrombosis Research*, vol. 114, no. 4, pp. 235–243, 2004.

[43] N. H. Wallén, A. H. Goodall, N. Li, and P. Hjemdahl, "Activation of haemostasis by exercise, mental stress and adrenaline: effects on platelet sensitivity to thrombin and thrombin generation," *Clinical Science*, vol. 97, no. 1, pp. 27–35, 1999.

[44] L. Nailin, N. H. Wallén, and P. Hjemdahl, "Evidence for prothrombotic effects of exercise and limited protection by aspirin," *Circulation*, vol. 100, no. 13, pp. 1374–1379, 1999.

[45] J.-S. Wang, C. J. Jen, H.-C. Kung, L.-J. Lin, T.-R. Hsiue, and H.-I. Chen, "Different effects of strenuous exercise and moderate exercise on platelet function in men," *Circulation*, vol. 90, no. 6, pp. 2877–2885, 1994.

[46] J.-S. Wang and S.-E. Chow, "Effects of exercise training and detraining on oxidized low-density lipoprotein-potentiated platelet function in men," *Archives of Physical Medicine and Rehabilitation*, vol. 85, no. 9, pp. 1531–1537, 2004.

[47] J.-S. Wang, C. J. Jen, and H.-I. Chen, "Effects of exercise training and deconditioning on platelet function in men," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 15, no. 10, pp. 1668–1674, 1995.

[48] J.-S. Wang, C. J. Jen, and H.-I. Chen, "Effects of chronic exercise and deconditioning on platelet function in women," *Journal of Applied Physiology*, vol. 83, no. 6, pp. 2080–2085, 1997.

[49] J.-S. Wang, C. F. Yang, and M.-K. Wong, "Effect of strenuous arm crank exercise on platelet function in patients with spinal cord injury," *Archives of Physical Medicine and Rehabilitation*, vol. 83, no. 2, pp. 210–216, 2002.

[50] J.-S. Wang, C. F. Yang, M.-K. Wong, S.-E. Chow, and J.-K. Chen, "Effect of strenuous arm exercise on oxidized-LDL-potentiated platelet activation in individuals with spinal cord injury," *Thrombosis and Haemostasis*, vol. 84, no. 1, pp. 118–123, 2000.

[51] J.-S. Wang, Y.-S. Li, J.-C. Chen, and Y.-W. Chen, "Effects of exercise training and deconditioning on platelet aggregation induced by alternating shear stress in men," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 25, no. 2, pp. 454–460, 2005.

[52] T. Kitai, M. Nishikawa, T. Tanigawa et al., "Inhibition by combined therapy with ticlopidine and aspirin of enhanced platelet aggregation during physical exercise in patients with coronary artery disease," *The American Heart Journal*, vol. 142, no. 2, article E1, 2001.

[53] F. Andreotti, G. A. Lanza, A. Sciahbasi et al., "Low-grade exercise enhances platelet aggregability in patients with obstructive coronary disease independently of myocardial ischemia," *American Journal of Cardiology*, vol. 87, no. 1, pp. 16–20, 2001.

[54] B. Harrison and M. Lordkipanidzé, "Clinical tests of platelet function," in *Platelets*, A. D. Michelson, Ed., 2012.

[55] H. Ikarugi, T. Taka, S. Nakajima et al., "Norepinephrine, but epinephrine, enhances platelet reactivity and coagulation after exercise in humans," *Journal of Applied Physiology*, vol. 86, no. 1, pp. 133–138, 1999.

[56] H. Ikarugi, M. Shibata, S. Shibata, H. Ishii, T. Taka, and J. Yamamoto, "High intensity exercise enhances platelet reactivity to shear stress and coagulation during and after exercise," *Pathophysiology of Haemostasis and Thrombosis*, vol. 33, no. 3, pp. 127–133, 2003.

[57] M. Bonifazi, A. M. Aloisi, I. Ceccarelli et al., "Platelet adhesion and aggregation on polyethylene: effect of exhaustive exercise," *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, vol. 68, no. 1, pp. 53–58, 2004.

[58] L. Cuzzolin, S. Lussignoli, F. Crivellente et al., "Influence of an acute exercise on neutrophil and platelet adhesion, nitric oxide plasma metabolites in inactive and active subjects," *International Journal of Sports Medicine*, vol. 21, no. 4, pp. 289–293, 2000.

[59] J.-S. Wang and L.-J. Cheng, "Effect of strenuous, acute exercise on α2-adrenergic agonist- potentiated platelet activation," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 19, no. 6, pp. 1559–1565, 1999.

[60] L. Rocker, W. K. Drygas, and B. Heyduck, "Blood platelet activation and increase in thrombin activity following a marathon race," *European Journal of Applied Physiology and Occupational Physiology*, vol. 55, no. 4, pp. 374–380, 1986.

[61] M. Hurlen, I. Seljeflot, and H. Arnesen, "Increased platelet aggregability during exercise in patients with previous myocardial infarction. Lack of inhibition by aspirin," *Thrombosis Research*, vol. 99, no. 5, pp. 487–494, 2000.

[62] W. K. Drygas, "Changes in blood platelet function, coagulation, and fibrinolytic activity in response to moderate, exhaustive, and prolonged exercise," *International Journal of Sports Medicine*, vol. 9, no. 1, pp. 67–72, 1988.

[63] R. B. Davis, D. G. Boyd, M. E. McKinney, and C. C. Jones, "Effects of exercise and exercise conditioning on blood platelet function," *Medicine and Science in Sports and Exercise*, vol. 22, no. 1, pp. 49–53, 1990.

[64] M. Möckel, N.-V. Ulrich, L. Röcker et al., "Exhaustive cycle exercise induces P-selectin expression, coagulation, and fibrinolysis activation in ultraendurance athletes," *Thrombosis Research*, vol. 94, no. 4, pp. 263–269, 1999.

[65] M. Möckel, N.-V. Ulrich, J. Heller et al., "Platelet activation through triathlon competition in ultra-endurance trained athletes: impact of thrombin and plasmin generation and catecholamine release," *International Journal of Sports Medicine*, vol. 22, no. 5, pp. 337–343, 2001.

[66] A.-A. Weber, H.-K. Heim, M. Schumacher, K. Schrör, and T. Hohlfeld, "Effects of selective cyclooxygenase isoform inhibition on systemic prostacyclin synthesis and on platelet function at rest and after exercise in healthy volunteers," *Platelets*, vol. 18, no. 5, pp. 379–385, 2007.

[67] E. Gkaliagkousi, E. Gavriilaki, E. Yiannaki et al., "Platelet activation in essential hypertension during exercise: pre- and post-treatment changes with an angiotensin ii receptor blocker," *American Journal of Hypertension*, vol. 27, no. 4, pp. 571–578, 2014.

[68] L. Röcker, S. Günay, H.-C. Gunga et al., "Activation of blood platelets in response to maximal isometric exercise of

the dominant arm," *International Journal of Sports Medicine*, vol. 21, no. 3, pp. 191–194, 2000.

[69] T. Hilberg, V. Schmidt, D. Gläser, D. Schammne, W. Lösche, and H. H. W. Gabriel, "Platelet activity, sensitivity to agonist, and platelet-leukocyte conjugate formation after long-term exercise," *Platelets*, vol. 13, no. 5-6, pp. 273–277, 2002.

[70] T. Hilberg, K. Menzel, D. Gläser, S. Zimmermann, and H. H. W. Gabriel, "Exercise intensity: platelet function and platelet-leukocyte conjugate formation in untrained subjects," *Thrombosis Research*, vol. 122, no. 1, pp. 77–84, 2008.

[71] T. Hilberg, E. Eichler, D. Gläser, V. Schmidt, and H. H. W. Gabriel, "Platelet activity, reactivity and platelet-leukocyte conjugate formation before and after exhaustive or moderate exercise in patients with IDDM," *Platelets*, vol. 15, no. 2, pp. 101–108, 2004.

[72] J. Constans, M. Seigneur, A. D. Blann et al., "Endothelial function, platelet activation and coagulation in lower limb occlusive arterial disease during treadmill exercise: correlations with transcutaneous oxygen pressure," *Thrombosis Research*, vol. 99, no. 6, pp. 557–561, 2000.

[73] C. R. Gibbs, A. D. Blann, E. Edmunds, R. D. S. Watson, and G. Y. H. Lip, "Effects of acute exercise on hemorheological, endothelial, and platelet markers in patients with chronic heart failure in sinus rhythm," *Clinical Cardiology*, vol. 24, no. 11, pp. 724–729, 2001.

[74] E. Shantsila, L. D. Tapp, B. J. Wrigley et al., "The effects of exercise and diurnal variation on monocyte subsets and monocyte-platelet aggregates," *European Journal of Clinical Investigation*, vol. 42, no. 8, pp. 832–839, 2012.

[75] V. Chaar, M. Romana, J. Tripette et al., "Effect of strenuous physical exercise on circulating cell-derived microparticles," *Clinical Hemorheology and Microcirculation*, vol. 47, no. 1, pp. 15–25, 2011.

[76] M. Sossdorf, G. P. Otto, R. A. Claus, H. H. W. Gabriel, and W. Lösche, "Cell-derived microparticles promote coagulation after moderate exercise," *Medicine and Science in Sports and Exercise*, vol. 43, no. 7, pp. 1169–1176, 2011.

[77] K. Maruyama, T. Kadono, and E. Morishita, "Plasma levels of platelet-derived microparticles are increased after anaerobic exercise in healthy subjects," *Journal of Atherosclerosis and Thrombosis*, vol. 19, no. 6, pp. 585–587, 2012.

[78] Y.-W. Chen, J.-K. Chen, and J.-S. Wang, "Strenuous exercise promotes shear-induced thrombin generation by increasing the shedding of procoagulant microparticles from platelets," *Thrombosis and Haemostasis*, vol. 104, no. 2, pp. 293–301, 2010.

[79] Y.-W. Chen, Y.-C. Chen, and J.-S. Wang, "Absolute hypoxic exercise training enhances in vitro thrombin generation by increasing procoagulant platelet-derived microparticles under high shear stress in sedentary men," *Clinical Science*, vol. 124, no. 10, pp. 639–649, 2013.

[80] J.-S. Wang, C. J. Jen, H.-L. Lee, and H.-I. Chen, "Effects of short-term exercise on female platelet function during different phases of the menstrual cycle," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 17, no. 9, pp. 1682–1686, 1997.

[81] L. M. Beaulieu and J. Freedman, "Inhibition of platelet function by the endothelium," in *Platelets*, A. D. Michelson, Ed., 2012.

[82] Y. Hellsten, M. Nyberg, L. G. Jensen, and S. P. Mortensen, "Vasodilator interactions in skeletal muscle blood flow regulation," *The Journal of Physiology*, vol. 590, no. 24, pp. 6297–6305, 2012.

[83] J. E. Freedman, J. Loscalzo, M. R. Barnard, C. Alpert, J. F. Keaney Jr., and A. D. Michelson, "Nitric oxide released from activated platelets inhibits platelet recruitment," *Journal of Clinical Investigation*, vol. 100, no. 2, pp. 350–356, 1997.

[84] J. E. Freedman, R. Sauter, E. M. Battinelli et al., "Deficient platelet-derived nitric oxide and enhanced hemostasis in mice lacking the NOSIII gene," *Circulation Research*, vol. 84, no. 12, pp. 1416–1421, 1999.

[85] J. S. Wang, C.-C. Lin, J.-K. Chen, and M.-K. Wong, "Role of chronic exercise in decreasing oxidized LDL-potentiated platelet activation by enhancing platelet-derived no release and bioactivity in rats," *Life Sciences*, vol. 66, no. 20, pp. 1937–1948, 2000.

[86] M. Yajima, S. Nomura, K. Namba, M. Sekine, T. Hosaka, and F. Numano, "Plasma thromboxane B2, 6-keto PGE(1α) and cyclic nucleotides levels as related to treadmill exercise test in patients with ischemic heart disease," *Japanese Circulation Journal*, vol. 49, no. 1, pp. 38–45, 1985.

[87] M. K. Todd, A. H. Goldfarb, and B. T. Boyer, "Effect of exercise intensity on 6-keto-PGF1 alpha, TXB2, and 6-keto-PGF1 alpha/TXB2 ratios," *Thrombosis Research*, vol. 65, no. 4-5, pp. 487–493, 1992.

[88] J. A. Zoladz, J. Majerczak, K. Duda, and S. Chłopicki, "Endurance training increases exercise-induced prostacyclin release in young, healthy men - Relationship with VO_{2max}," *Pharmacological Reports*, vol. 62, no. 3, pp. 494–502, 2010.

[89] F. Suhr, J. Brenig, R. Müller, H. Behrens, W. Bloch, and M. Grau, "Moderate exercise promotes human RBC-NOS activity, NO production and deformability through Akt kinase pathway," *PLoS ONE*, vol. 7, no. 9, Article ID e45982, 2012.

[90] G. S. Kansas, G. S. Wood, and T. F. Tedder, "Expression, distribution, and biochemistry of human CD39: role in activation-associated homotypic adhesion of lymphocytes," *The Journal of Immunology*, vol. 146, no. 7, pp. 2235–2244, 1991.

[91] K. Koziak, J. Sévigny, S. C. Robson, J. B. Siegel, and E. Kaczmarek, "Analysis of CD39/ATP diphosphohydrolase (ATPDase) expression in endothelial cells, platelets and leukocytes," *Thrombosis and Haemostasis*, vol. 82, no. 5, pp. 1538–1544, 1999.

[92] H. Zimmermann, "5*I*-nucleotidase: molecular structure and functional aspects," *Biochemical Journal*, vol. 285, part 2, pp. 345–365, 1992.

[93] T. Mann, R. P. Lamberts, and M. I. Lambert, "Methods of prescribing relative exercise intensity: physiological and practical considerations," *Sports Medicine*, vol. 43, no. 7, pp. 613–625, 2013.

[94] A. D. Michelson, P. A. Ellis, M. R. Barnard, G. B. Matic, A. F. Viles, and A. S. Kestin, "Downregulation of the platelet surface glycoprotein Ib-IX complex in whole blood stimulated by thrombin, adenosine diphosphate, or an in vivo wound," *Blood*, vol. 77, no. 4, pp. 770–779, 1991.

[95] P. Hourdille, E. Heilmann, R. Combrie, J. Winckler, K. J. Clemetson, and A. T. Nurden, "Thrombin induces a rapid redistribution of glycoprotein Ib-IX complexes within the membrane systems of activated human platelets," *Blood*, vol. 76, no. 8, pp. 1503–1513, 1990.

[96] A. D. Michelson, J. D. Wencel-Drake, A. S. Kestin, and M. R. Barnard, "Platelet activation results in a redistribution of glycoprotein IV (CD36)," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 14, no. 7, pp. 1193–1201, 1994.

[97] C. M. Albert, M. A. Mittleman, C. U. Chae, I.-M. Lee, C. H. Hennekens, and J. E. Manson, "Triggering of sudden death from cardiac causes by vigorous exertion," *The New England Journal of Medicine*, vol. 343, no. 19, pp. 1355–1361, 2000.

[98] M. S. El-Sayed, A. Younesian, K. Rahman, F. M. Ismail, and Z. E.-S. Ali, "The effects of arm cranking exercise and training on

platelet aggregation in male spinal cord individuals," *Thrombosis Research*, vol. 113, no. 2, pp. 129–136, 2004.

[99] R. Rauramaa, J. T. Salonen, K. Seppanen, J. M. Venäläinen, M. Ihanainen, and V. Rissanen, "Inhibition of platelet aggregability by moderate-intensity physical exercise: a randomized clinical trial in overweight men," *Circulation*, vol. 74, no. 5, pp. 939–944, 1986.

[100] L. R. de Meirelles, A. C. Mendes-Ribeiro, M. A. P. Mendes et al., "Chronic exercise reduces platelet activation in hypertension: upregulation of the L-arginine-nitric oxide pathway," *Scandinavian Journal of Medicine and Science in Sports*, vol. 19, no. 1, pp. 67–74, 2009.

[101] C. Di Massimo, P. Scarpelli, M. Penco, and M. G. Tozzi-Ciancarelli, "Possible involvement of plasma antioxidant defences in training-associated decrease of platelet responsiveness in humans," *European Journal of Applied Physiology*, vol. 91, no. 4, pp. 406–412, 2004.

[102] E. Arosio, P. Minuz, M. Prior et al., "Vascular adhesion molecule-1 and markers of platelet function before and after a treatment with iloprost or a supervised physical exercise program in patients with peripheral arterial disease," *Life Sciences*, vol. 69, no. 4, pp. 421–433, 2001.

[103] G. Lippi, M. Montagnana, G. L. Salvagno, M. Franchini, and G. C. Guidi, "Comparison of platelet function between sedentary individuals and competitive athletes at rest," *Thrombosis Journal*, vol. 4, article 10, 2006.

[104] D. M. Bramble and D. E. Lieberman, "Endurance running and the evolution of Homo," *Nature*, vol. 432, no. 7015, pp. 345–352, 2004.

[105] D. H. J. Thijssen, E. A. Dawson, M. A. Black, M. T. E. Hopman, N. T. Cable, and D. J. Green, "Brachial artery blood flow responses to different modalities of lower limb exercise," *Medicine and Science in Sports and Exercise*, vol. 41, no. 5, pp. 1072–1079, 2009.

[106] S. Mohan, K. Koyoma, A. Thangasamy, H. Nakano, R. D. Glickman, and N. Mohan, "Low shear stress preferentially enhances IKK activity through selective sources of ROS for persistent activation of NF-κB in endothelial cells," *The American Journal of Physiology—Cell Physiology*, vol. 292, no. 1, pp. C362–C371, 2007.

[107] B. M. Prior, P. G. Lloyd, J. Ren et al., "Arteriogenesis: role of nitric oxide," *Endothelium*, vol. 10, no. 4-5, pp. 207–216, 2003.

[108] D. J. Green, A. Spence, N. Rowley, D. H. J. Thijssen, and L. H. Naylor, "Vascular adaptation in athletes: is there an 'athlete's artery'?" *Experimental Physiology*, vol. 97, no. 3, pp. 295–304, 2012.

[109] M. J. Durand and D. D. Gutterman, " Exercise and vascular function: how much is too much? " *Canadian Journal of Physiology and Pharmacology*, vol. 92, no. 7, pp. 551–557, 2014.

[110] S. N. Willich, M. Lewis, H. Lowel et al., "Physical exertion as a trigger of acute myocardial infarction," *The New England Journal of Medicine*, vol. 329, no. 23, pp. 1684–1690, 1993.

[111] D. S. Siscovick, "Exercise and its role in sudden cardiac death," *Cardiology Clinics*, vol. 15, no. 3, pp. 467–472, 1997.

[112] D. S. Siscovick, N. S. Weiss, R. H. Fletcher, and T. Lasky, "The incidence of primary cardiac arrest during vigorous exercise," *The New England Journal of Medicine*, vol. 311, no. 14, pp. 874–877, 1984.

[113] M. A. Mittleman, M. Maclure, G. H. Tofler, J. B. Sherwood, R. J. Goldberg, and J. E. Muller, "Triggering of acute myocardial infarction by heavy physical exertion—protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators," *The New England Journal of Medicine*, vol. 329, no. 23, pp. 1677–1683, 1993.

[114] H. Khan, S. Kunutsor, R. Rauramaa et al., "Cardiorespiratory fitness and risk of heart failure: a population-based follow-up study," *European Journal of Heart Failure*, vol. 16, no. 2, pp. 180–188, 2014.

[115] P. Kokkinos and J. Myers, "Exercise and physical activity: clinical outcomes and applications," *Circulation*, vol. 122, no. 16, pp. 1637–1648, 2010.

[116] D. E. R. Warburton, C. W. Nicol, and S. S. D. Bredin, "Health benefits of physical activity: the evidence," *Canadian Medical Association Journal*, vol. 174, no. 6, pp. 801–809, 2006.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 920356, 9 pages
http://dx.doi.org/10.1155/2015/920356

Research Article

Impaired Circulating Angiogenic Cells Mobilization and Metalloproteinase-9 Activity after Dynamic Exercise in Early Metabolic Syndrome

Natalia G. Rocha,[1] Allan R. K. Sales,[1] Leticia A. Penedo,[1] Felipe S. Pereira,[1] Mayra S. Silva,[1] Renan L. Miranda,[1] Jemima F. R. Silva,[1] Bruno M. Silva,[2] Aline A. Santos,[1] and Antonio C. L. Nobrega[1]

[1]*Laboratory of Exercise Sciences, Department of Physiology and Pharmacology, Fluminense Federal University, 24210-130 Niterói, RJ, Brazil*
[2]*Department of Physiology, Section of Exercise Physiology, Federal University of São Paulo, 04023-062 São Paulo, SP, Brazil*

Correspondence should be addressed to Antonio C. L. Nobrega; anobrega@id.uff.br

Received 24 March 2015; Revised 22 May 2015; Accepted 25 May 2015

Academic Editor: Pasquale Pagliaro

Increased levels of adhesion molecules or metalloproteinases (MMPs) may indicate endothelial dysfunction. Exercise mobilizes circulating angiogenic cells (CACs) from bone marrow in healthy subjects, improving vascular function. However, it is unclear whether this mechanism is preserved in the early stages of metabolic syndrome (early MetS). We aimed to evaluate the acute effects of exercise on adhesion molecules, angiogenic factors, MMPs, and CACs in early MetS. Fifteen subjects with early MetS and nine healthy controls underwent an exercise session and a nonexercise session, randomly. Adhesion molecules, angiogenic factors, CACs, and MMPs were evaluated before and after exercise or nonexercise sessions. At baseline, levels of sE-selectin, sICAM-1, and MMP-9 were higher in early MetS than in controls ($P \leq 0.03$). After exercise, sE-selectin, sICAM-1, and MMP-9 levels were still higher in early MetS ($P < 0.05$). Subjects with early MetS presented less CACs ($P = 0.02$) and higher MMP-9 activity ($P \leq 0.04$), while healthy controls presented higher MMP-2 activity after exercise. There was no difference between moments in nonexercise session ($P > 0.05$). In conclusion, subjects with early MetS already presented impaired endothelial function at rest along with a decrease in CACs and an increase in MMP-9 activity in response to exercise.

1. Introduction

Cardiovascular disease is the major cause of death worldwide [1]. Mechanisms underlying atherosclerosis are tightly related to the presence of cardiometabolic risk factors. The incidence of metabolic syndrome (MetS) has been increasing in the global population [2]. MetS is characterized by a cluster of metabolic disorders, including dysglycemia, dyslipidemia, obesity, and hypertension [3]. In the early stages of MetS development (early MetS), when no chronic diseases are yet present and no drug therapy has been used, it may be possible to determine an increased risk of atherogenesis by assessing endothelial dysfunction [4].

The intact endothelium prevents leukocyte migration into the vessel wall. This leukocyte interaction with the endothelium is regulated by the expression of cell adhesion molecules, such as endothelial leukocyte adhesion molecule (E-selectin), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [5]. Imbalance expression of cell adhesion molecules is referred to as endothelial dysfunction [6] and is usually present in patients with MetS [7].

Circulating angiogenic cells (CACs) are usually recruited from the bone marrow to peripheral blood promoting neovasculogenesis, maintaining vascular integrity. Despite being controversial, studies have shown associations between

chronic diseases, such as hypertension [8], diabetes [9], and dyslipidemia [10], and the number/functionality of CACs. Jialal et al. [11] showed a reduced number of CACs along with impaired functionality in subjects with MetS, who were using antihypertensive drugs. However, some drugs, such as antihypertensives and statins, are already known to influence the number and/or functionality of CACs [12, 13]. Thus, whether the number of CACs is already altered in drug naïve subjects with MetS is unclear.

Acute exercise provokes a transient inflammatory response through the increase in the amounts of several cytokines, angiogenic factors [14], and matrix metalloproteinases (MMPs) in the circulation [15]. MMP-2 and MMP-9 are related to inflammation, angiogenesis, wound healing, and cell migration, including CACs migration from the bone marrow to peripheral blood [16]. Subjects with established MetS-related diseases present high levels of proinflammatory markers and MMP-9 [16]. In addition, a maximal aerobic exercise seems to increase CACs in patients with coronary artery disease but less than in healthy subjects [17]. However, the acute effects of exercise on CACs and MMPs in subjects with MetS and without chronic diseases are still unknown.

This study aimed to evaluate the effects of a single bout of exercise on adhesion molecules, on angiogenic factors, on CACs, and on MMPs in subjects with early MetS. We hypothesized that subjects with early MetS, that is, free of overt disease and without using medications, already present an impaired endothelial function at baseline along with an altered response of angiogenic factors, CACs, and MMPs to exercise.

2. Materials and Methods

2.1. Ethical Approval. This study protocol was approved by the ethical committee of Antonio Pedro University Hospital, according to the latest revision of the Declaration of Helsinki. All subjects gave written informed consent before their participation in the study.

2.2. Subjects. Subjects were recruited through advertisements at the university and in local newspapers. Twenty-four subjects were enrolled, fifteen subjects with early MetS (MetS group, age: 37 ± 2 years old) and nine healthy subjects (controls) with none of the five criteria for MetS (healthy group, age: 33 ± 3 years old). The MetS group presented at least three of the following five criteria defined by the American Heart Association [3]: waist circumference >90 cm (men) or >80 cm (women); systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; fasting glucose ≥5.6 mmol·L^{-1}; triglycerides ≥1.7 mmol·L^{-1}; high-density lipoprotein cholesterol (HDL-c) <1 mmol·L^{-1} (men) or <1.3 mmol·L^{-1} (women). Other inclusion criteria included the absence of any diagnosed disease, no recent infection, no medication, nonsmoker, woman with regular menstrual cycle, and sedentary lifestyle (not attended exercise program lasting ≥30 min, three times per week during the last three months). Women had regular menstrual cycles and were evaluated in the early follicular phase (up to 5th day of menstrual cycle). The eligibility requirements were determined through clinical history assessment, physical examination, blood pressure measurement, biochemical blood analyses, resting electrocardiogram, and peak cardiopulmonary exercise testing.

2.3. Biochemical Blood Analyses. Blood was drawn from an anterior cubital vein in the morning after a 12-hour overnight fast. Cholesterol and its subfractions (HDL-c and low-density lipoprotein (LDL-c)) as well as triglycerides and glucose were determined using enzymatic colorimetric methods. Plasma insulin was measured by electrochemiluminescence immunoassay. Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) derived from fasting glucose and insulin concentrations [18]. Total leukocyte count was measured by an electronic counter, the HST-302N system.

2.4. Clinical Evaluation. A physician performed the evaluation, including clinical history assessment and resting electrocardiogram (CardioCare 2000; Bionet, Tustin, CA, USA). Resting blood pressure measurements were performed twice, one on each arm, on two separate days in the upright sitting position. Recordings were made under quiet and temperature controlled (approximately 24°C) conditions. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) was used.

2.5. Physical Examination. Anthropometric variables, such as weight and height, were measured using a medical beam balance (Welmy; Santa Bárbara d'Oeste, SP, Brazil). Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Waist circumference was considered the midpoint between the iliac crest and the last floating rib (XII rib).

2.6. Cardiopulmonary Exercise Testing. Subjects underwent a cardiopulmonary exercise test, performed until fatigue on a cycle ergometer (CG400 model, Inbrasport; Porto Alegre, RS, Brazil). The protocol was developed according to predicted maximal exercise capacity. Subjects were verbally encouraged to exercise until exhaustion in order to reach volitional fatigue at approximately 10 min of testing. Ventilation, oxygen uptake, and carbon dioxide output were determined with each breath (CPX Ultima Gas Exchange System, Medgraphics Corp.; St. Paul, MN, USA). An electrocardiogram was monitored through 12 leads (Welch Allyn CardioPerfect Workstation, Welch Allyn; Skaneateles Falls, NY, USA), and perceived exertion was verified every minute using the 0–10 Borg scale. Breath-by-breath ventilation and expired gas data were averaged to 20 s to identify the peak oxygen consumption (VO_{2peak}), which was considered the highest value of oxygen uptake recorded during exercise. Ventilatory threshold was identified by combination of the following methods: (1) inflection of ventilation versus time curve and (2) consistent increase in the ventilatory equivalent of oxygen (VE/VO_2) without a concomitant increase ventilatory equivalent of carbon dioxide (VE/VCO_2).

2.7. Experimental Protocol. On two separate days, at least two days apart, subjects from both the healthy and MetS groups

underwent the exercise session and nonexercise session in a random order. Adhesion molecules, MMP-9 ($n = 24$), and CACs ($n = 18$) were evaluated before and 10 min after the exercise or nonexercise session. During the nonexercise session, subjects sat still on the cycler ergometer for the same period of time as the exercise session. These experimental sessions were always conducted at the same time of the day after a 1-hour fast. Participants were also given standard feeding orientations for the previous day and asked to abstain from caffeine and alcohol consumption and physical exercise for at least 48 h.

2.8. Exercise Session. An individualized continuous submaximal bout of exercise was performed for 40 min on a cycle ergometer (CG400 model, Inbrasport; Porto Alegre, RS, Brazil) at an intensity corresponding to 80% of the ventilatory threshold, which was observed in the previous peak cardiopulmonary exercise test. This exercise was preceded by a warm-up of five minutes, pedaling at 30 W, followed by five minutes of recovery pedaling at 30 W. Breath-by-breath ventilation and expired gas were recorded throughout the exercise bout by a digital metabolic analyzer (CPX Ultima Gas Exchange System, Medgraphics Corp.; St. Paul, MN, USA), which was linked to a computer for data recording and offline analysis.

2.9. Concentration of Adhesion Molecules, MMP-9, and Angiogenic Factors. The levels of sE-selectin, sICAM-1, sVCAM-1, MMP-9, vascular endothelial growth factor (VEGF), granulocyte-colony stimulating factor (G-CSF), and granulocyte macrophage-colony stimulating factor (GM-CSF) were determined using a multiplex sandwich immunoassay that was performed using a Luminex 200 (Luminex; Austin, USA) and xMAP technology [19, 20]. In this assay, the specific antibody was covalently coupled to Luminex microspheres and uniquely labeled with a fluorescent dye. Briefly, the microspheres were incubated overnight with standards, controls, and serum samples in a 96-well microliter filter plate for duplicate determination. After washing the wells, a mixture of the relevant biotinylated detection antibodies was added and incubated for 30 min at room temperature. Streptavidin-phycoerythrin was then added for an additional 30 min. The beads were finally washed twice, resuspended in buffer, and analyzed by Exponent software according to the manufacturer's instructions. The results are reported as the means of the duplicates.

2.10. Circulating Angiogenic Cells. Peripheral blood mononuclear cells (PBMC) were isolated from the blood by Ficoll density-gradient centrifugation, according to the manufacturer's instructions. After the isolation, 5×10^6 cells were incubated with 10 μL of CD34-FITC (BD Biosciences; Franklin Lakes, NJ, USA), 6 μL of CD133-PE (Miltenyi; Bergisch Gladbach, North Rhine-Westphalia, Germany), and 10 μL of VEGFR2-APC (R&D Systems; Minneapolis, MN, USA). All antibodies were added directly to the cell suspension and kept in the dark at 4°C for 40 min. Cells were washed three times with phosphate buffer solution and fixed with FACS Lysing solution (BD Biosciences; Franklin Lakes, NJ, USA). The respective isotypes (FITC, PE, and APC) were used as controls. Cell fluorescence was measured by flow cytometry using FACSVerse (BD Biosciences; Franklin Lakes, NJ, USA), and a total of 3×10^6 events were analyzed using the Suits software (BD Biosciences; Franklin Lakes, NJ, USA). $CD34^+/VEGFR2^+$ cells and $CD34^+/CD133^+/VEGFR2^+$ cells were considered CACs. They were calculated as a percentage of $VEGFR2^+$ cells and $CD133^+/VEGFR2^+$ cells in the $CD34^+$ gate, respectively. Intraclass correlation coefficient was 0.80 for $CD34^+/VEGFR2^+$ cells and 0.90 for $CD34^+/CD133^+/VEGFR2^+$ cells.

2.11. Gelatin Zymography. Gelatinolytic activity of serum MMP-2 and MMP-9 was measured using the gelatin zymography technique. Quantification of serum protein was determined by the Lowry method [21]. Proteins were electrophoresed through a 9% polyacrylamide gel copolymerized with gelatin (2 mg/mL, type A from porcine skin; Sigma-Aldrich, St. Louis, MO, USA) and a 4% polyacrylamide stacking gel. The gels were washed with 2.5% Triton X-100 and incubated for 24 h at 37°C in activation buffer (10 mM Tris buffer, pH 7.5, with 5 mM $CaCl_2$ and 1 μM $ZnCl_2$) in order to verify the activity of the enzyme. After incubation, the gels were stained with a solution containing 30% methanol, 10% acetic acid, and 0.05% Coomassie brilliant blue (R-250; Sigma-Aldrich, St. Louis, MO, USA). Gelatinolytic activities were defined as transparent bands against the dark blue background. Zymograms were digitally scanned. The band intensities were measured using Scion Image (Scion Corporation; Frederick, MD, USA) and expressed as a ratio to the internal standard. Fetal bovine serum was used in each gel as a molecular weight standard for gelatinases and as an internal standard to correct for intergel variability.

2.12. Statistical Analysis. Data distribution was determined through the Shapiro-Wilk test and homogeneity of variances by Levene's test. A total sample size of 8 subjects was necessary to detect differences of 5% between groups (group main effect), considering a two-way ANOVA P value of 0.05 and power of 0.80. Unpaired Student's t-test was performed to identify significance between group differences in all normally distributed variables. When distributional assumption of normality was not met, the statistical inference was obtained using the Mann-Whitney U test, an equivalent nonparametric test. A chi-square test was used to analyze categorical variables. Two-way ANOVA was used to compare the variables before and after exercise or nonexercise session between the groups, followed by Fisher post hoc test in case of significant interaction, group, and/or moment effect. All the concentration values of adhesion molecules were multiplied by a constant 100. Outliers were considered as the mean ± three times the standard deviation and were excluded from the analyses. Significance was accepted at the 0.05 level.

3. Results

The anthropometric, clinical, and biochemical profiles of healthy controls and subjects with early MetS are presented in Table 1. As expected, body mass, body mass index (BMI),

Table 1: Selected subject characteristics.

Variable	Healthy	MetS	P value
Number	9	15	—
Age, yr	33 ± 3	37 ± 2	0.23
Sex, M/W	6/3	12/3	0.47
Body mass, kg	71 ± 4	93 ± 4	<0.01
BMI, $kg \cdot m^{-2}$	23 ± 1	31 ± 1	<0.01
Body fat, %	26 ± 2	36 ± 2	<0.01
Waist circumference, cm	79 ± 3	102 ± 3	<0.01
Systolic BP, mmHg	117 ± 2	126 ± 3	<0.01
Diastolic BP, mmHg	75 ± 2	84 ± 2	<0.01
VO_{2peak}, $L \cdot min^{-1}$	2.3 ± 0.2	2.2 ± 0.3	0.74
Total cholesterol, $mmol \cdot L^{-1}$	4.4 ± 0.2	5.6 ± 0.2	<0.01
LDL cholesterol, $mmol \cdot L^{-1}$	2.7 ± 0.2	3.6 ± 0.2	<0.01
HDL cholesterol, $mmol \cdot L^{-1}$*	1.3 ± 0.5	1 ± 0.2	<0.01
Triglycerides, $mmol \cdot L^{-1}$	0.7 ± 0.1	2.1 ± 0.2	<0.01
Glucose, $mmol \cdot L^{-1}$	4.8 ± 0.1	5.5 ± 0.2	<0.01
Insulin, $\mu IU \cdot mL^{-1}$*	7.4 ± 2.5	13.8 ± 12.5	<0.01
HOMA-IR*	1.5 ± 1.0	3.0 ± 3.5	<0.01
Total leukocytes count, $10^3 \cdot mm^{-3}$	6.2 ± 0.8	6.8 ± 0.4	0.44

Values are means ± SE or *medians ± interquartile range. M: men; W: women; BMI: body mass index; BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis model of insulin resistance.

body fat, waist circumference, blood pressure, lipid profile, and glucose profile were significantly different between the healthy and MetS groups. There was no difference between groups regarding gender, age, absolute peak oxygen consumption (VO_{2peak}), and total leukocyte count.

Figure 1 shows the levels of adhesion molecules (sE-selectin, sICAM-1, and sVCAM-1) before and after exercise in healthy controls and subjects with early MetS. Levels of sE-selectin and sICAM-1 were 106% and 87% higher in subjects with early MetS when compared with healthy controls ($P < 0.01$; Figure 1) at baseline. After exercise, the levels of these molecules were still higher than in healthy controls ($P \leq 0.01$). sVCAM-1 levels were similar between groups at baseline ($P = 0.83$) and after exercise ($P = 0.76$). However, both groups presented increased sVCAM-1 levels after exercise ($P \leq 0.03$).

Regarding the flow cytometry data (Figure 2), no difference was found at baseline in either $CD34^+/VEGFR2^+$ cells ($P = 0.31$; Figure 2(a)) or $CD34^+/CD133^+/VEGFR2^+$ cells ($P = 0.39$; Figure 2(b)) between groups. Subjects with early MetS showed a lower number of $CD34^+/VEGFR2^+$ cells ($P = 0.02$) and $CD34^+/CD133^+/VEGFR2^+$ cells ($P = 0.02$) than healthy controls after exercise.

Subjects with early MetS presented higher levels of MMP-9 at baseline ($P = 0.04$) and after exercise ($P = 0.02$) when compared to healthy controls (Table 2). Although G-CSF have increased similarly in both groups after exercise ($P < 0.05$), no differences were observed in the serum concentration of all angiogenic factors between groups before and after exercise ($P > 0.05$; Table 2).

Figure 3 shows the MMP-2 and MMP-9 activities before and after exercise sessions in healthy controls and subjects with early MetS. At baseline, no differences were found in MMP-2 and MMP-9 activities between groups ($P > 0.05$; Figures 3(a) and 3(b), resp.). After exercise, only healthy controls had increased MMP-2 activity after exercise ($P < 0.01$; Figure 3(a)). In addition, subjects with early MetS presented an increase in MMP-9 activity after exercise ($P = 0.01$; Figure 3(b)), which was different between groups ($P < 0.05$; Figure 3(b)).

There was no difference in all variables between moments in nonexercise session ($P > 0.05$; data not shown).

4. Discussion

Our study hypothesized that subjects with early MetS already presented an impaired endothelial function along with an altered response of angiogenic factors, CACs, and MMPs to exercise. This study presented four novel findings: (1) subjects with early MetS presented higher levels of adhesion molecules and MMP-9 and similar levels of $CD34^+/VEGFR2^+$ and $CD34^+/CD133^+/VEGFR2^+$ cells at baseline compared with healthy controls; (2) subjects with early MetS presented a lower number of $CD34^+/VEGFR2^+$ and $CD34^+/CD133^+/VEGFR2^+$ cells after exercise; (3) healthy controls presented increased MMP-2 activity, while subjects with early MetS presented higher MMP-9 activity after exercise; and (4) no differences were observed in angiogenic factors between groups before and after exercise.

Adhesion molecules play a critical role during inflammatory responses by mediating the interaction of leukocytes to endothelial cells and, subsequently, their migration into perivascular tissues [22]. Studies have associated high levels of cell adhesion molecules with endothelial dysfunction and the development of atherosclerosis [23]. It was also demonstrated that subjects with early MetS already present an increased brachial artery time to peak diameter and a reduced shear rate-adjusted flow-mediated dilation [24], which may represent independent markers of endothelial function in subjects with early MetS. The present study corroborated these findings, showing that subjects with early MetS presented increased baseline levels of sE-selectin and sICAM-1 and, consequently, early endothelial dysfunction. As observed for adhesion molecules, the levels of MMP-9 seemed to be higher in subjects with early MetS, while MMPs activities were not. Some studies have demonstrated that increased baseline level of MMP-9 is related to atherothrombotic risk in subjects with cardiometabolic diseases [25] and in healthy subjects [26].

Differences between the groups regarding $CD34^+/VEGFR2^+$ and $CD34^+/CD133^+/VEGFR2^+$ cells were observed after exercise. This fact could be partially explained by an elevated proinflammatory state [27]. In fact, levels of sE-selectin and sICAM-1 were still increased after exercise in subjects with early MetS, which contributes to apoptosis or loss of CACs functionality. Acute exercise induces a transient inflammatory response through the increase in several cytokines such as interleukin-6, tumor necrosis factor-α, C-reactive protein [14], and nuclear factor kappa

Table 2: Serum concentration of MMP-9 and angiogenic factors before and after exercise.

Variables	Healthy		MetS	
	Before exercise	After exercise	Before exercise	After exercise
MMP-9 ($ng \cdot mL^{-1}$)	1.6 ± 0.3	1.8 ± 0.3	2.3 ± 0.2*	2.6 ± 0.2*
VEGF ($pg \cdot mL^{-1}$)	225.1 ± 65.3	241.6 ± 65.8	146.6 ± 46.1	155.5 ± 46.5
G-CSF ($pg \cdot mL^{-1}$)	11.8 ± 3.7	15.8 ± 4.6†	17.3 ± 2.9	21.3 ± 3.6†
GM-CSF ($pg \cdot mL^{-1}$)	1.3 ± 1.2	1.6 ± 1.1	2.6 ± 0.9	3.3 ± 0.9

Values are means ± SE. Healthy: healthy controls; MetS: subjects with metabolic syndrome; MMP-9: metalloproteinase-9; VEGF: vascular endothelial growth factor; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte macrophage-colony stimulating factor. *$P \leq 0.04$ versus healthy controls; †$P < 0.05$ versus before exercise.

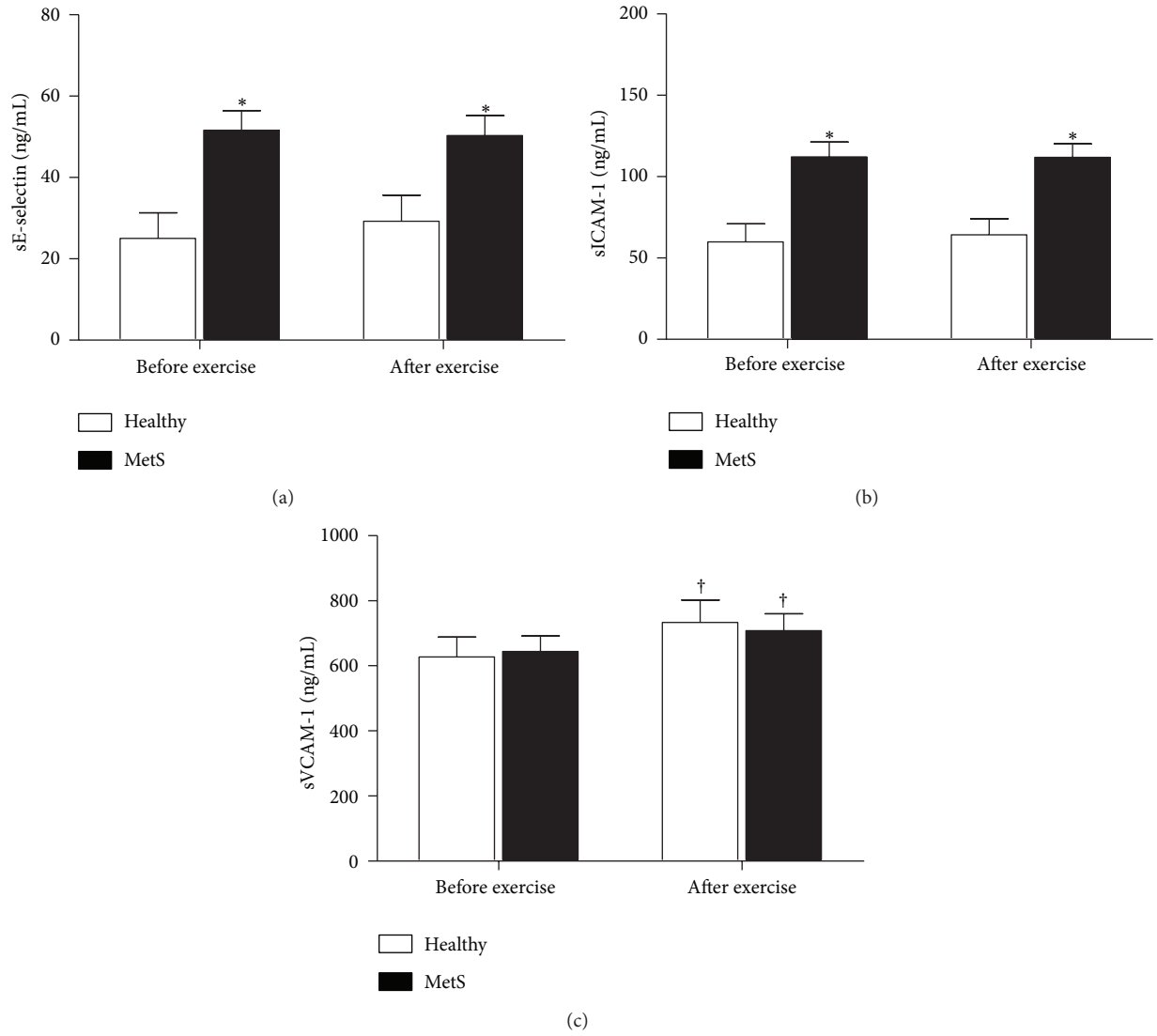


Figure 1: Adhesion molecules in healthy controls and subjects with MetS before and after exercise. sE-selectin: soluble endothelial selectin; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1. *$P \leq 0.01$ versus healthy controls; †$P \leq 0.03$ versus before exercise.

B [28] and oxidative stress [29] in healthy subjects and in subjects with coronary artery disease [30]. In contrast, chronic repetitive exercise, that is, physical training, induces the development of an adaptation to the acute stress of exercise bouts [31] and reduces proinflammatory cytokine basal levels while inducing the expression of antioxidant and anti-inflammatory variables in the vessel [30]. These factors may directly inhibit the development of atherosclerosis and, consequently, diminish the risk of cardiovascular events [32].

Previous studies have shown that chronic exercise increases the number of CACs in subjects with MetS [33, 34]. However, these subjects presented established diseases, such

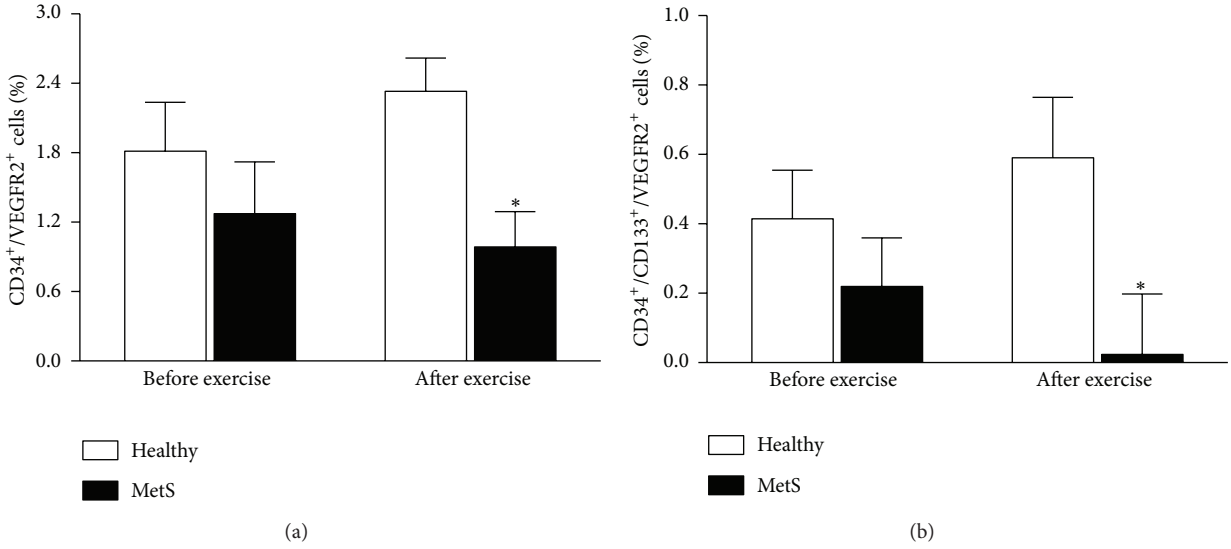


Figure 2: Circulating angiogenic cells ((a) $CD34^+/VEGFR2^+$ cells; (b) $CD34^+/CD133^+/VEGFR2^+$ cells) before and after exercise in healthy controls and subjects with MetS. $^*P = 0.02$ versus healthy controls.

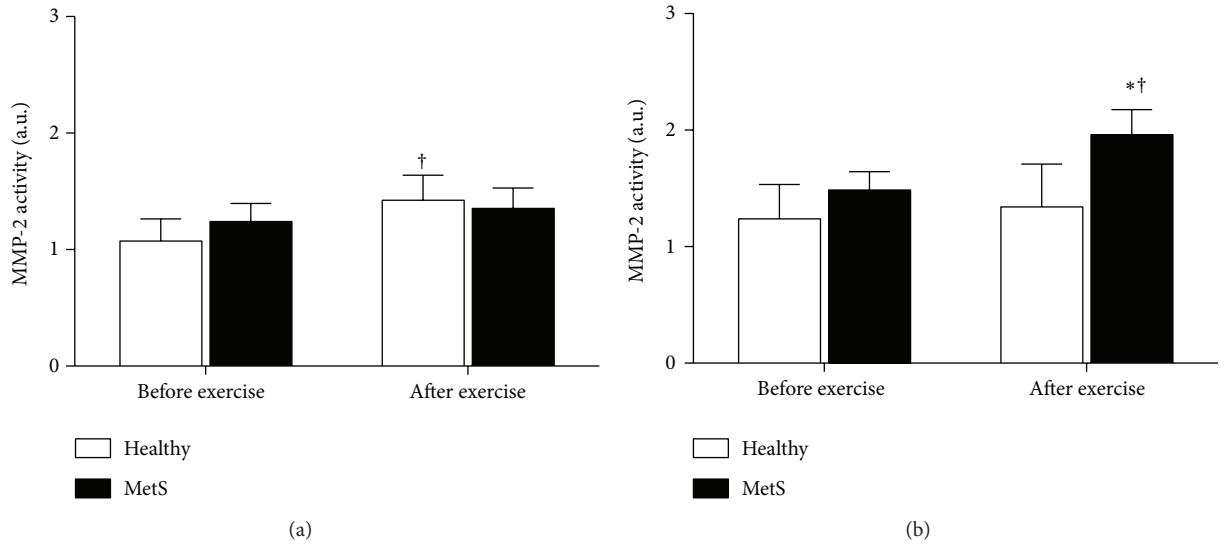


Figure 3: MMP-2 (a) and MMP-9 (b) activities before and after exercise in healthy controls and subjects with MetS. MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9. $^*P < 0.05$ versus healthy controls; $^\dagger P \leq 0.01$ versus before exercise.

as hypertension, diabetes, and coronary artery disease, and were under the effect of different medications. Therefore, the results of those studies could be biased by the presence of cardiometabolic diseases or the pleiotropic effects of the drugs. To our knowledge, the present study is the first to investigate the number of CACs after one bout of exercise in subjects with early MetS, that is, free of overt disease or pharmacological treatment.

An exercise bout increased MMP-2 activity in healthy controls and MMP-9 activity in subjects with early MetS. A previous study has already demonstrated opposite behaviors between serum MMP-2 and MMP-9 in critical limb ischemia patients [35]. It was also shown that expression of MMP-2 and MMP-9 on CACs surface plays a role in their invasive capacity and the guidance of circulating endothelial cells (mature or progenitor) to ischemic regions. Exercise is a physiological stimulus, which increases local production and release of growth factors and chemoattractant cytokines [36, 37]. These factors are able to activate MMPs, causing CACs mobilization from bone marrow to peripheral circulation [36–38]. It was shown that G-CSF is able to increase MMP-2 activity in human trophoblast cell line, through activation of PI3K/Akt and Erk signaling pathways [38]. Although subjects with early MetS also presented increased levels of G-CSF after exercise,

they failed to increase MMP-2 activity and release CACs to peripheral blood. Other studies are necessary to address possible mechanisms that activate MMP-2 in MetS.

In addition, MMP-9 is released from skeletal muscles into the circulation as a response to proinflammatory conditions, contributing to the disruption of atherosclerotic plaques [39]. It was already shown that concentration and activity of MMP-9 increased during exercise in healthy subjects, returning to baseline levels at the end of exercise [15]. Our results corroborated these findings, showing that there is no difference between the pre- and postexercise moments in healthy controls. On the other hand, it seems that subjects with early MetS exhibited a sustained or late increase in MMP-9 activity after exercise. MMP-9 high levels and activity have been considered independent predictors for the development of coronary artery diseases [16] and are associated with increased cardiovascular risk in subjects with MetS [40].

CACs and MMP-9 may be considered independent biomarkers for endothelial function, predicting the onset of MetS-related diseases. Although the activation of proteinases, such as MMP-9, increases CACs mobilization from the bone marrow quiescent niche [41], the increase in MMP-9 activity was not enough to increase CACs in subjects with early MetS. It is conceivable that MMP-9 high activity, after exercise in subjects with early MetS, may have led to a transitory increase in CACs mobilization from the bone marrow to peripheral blood followed by an increase in CACs consumption by the impaired endothelium in subjects with early MetS. However, other specific studies are necessary to confirm these hypotheses. Moreover, there are other molecules and conditions, such as nitric oxide and oxidative stress, which could influence the number of CACs after exercise. NO is already known as a potent stimulus of CACs mobilization. A lower bioavailability of serum NO after exercise would be a mechanism that may explain the diminished levels of CACs in subjects with early MetS. It was also shown that antioxidative enzyme levels are reduced [42], while oxidative stress is increased in subjects with MetS [42] or after acute exercise [29].

The present study should be interpreted considering some limitations. First, anti-CD34, anti-VEGFR2, and anti-CD133 antibodies were used to quantify CACs by flow cytometry. Currently, there is no gold-standard marker for characterization of CACs. This point makes it difficult to standardize and compare the quantification of CACs among the different published studies. However, $CD34^+/VEGFR2^+$ and $CD34^+/CD133^+/VEGFR2^+$ are most frequently used for their identification because the level of circulating $CD34^+/VEGFR2^+$ cells predicts the occurrence of cardiovascular events and death, which may help to identify patients at increased cardiovascular risk [43]. Second, we used men and women in the same analysis. To counter this limitation, the groups were matched for sex differences and all the women were evaluated in the follicular phase of the menstrual cycle. A third potential limitation was the absence of differences in CACs number at baseline between the groups. Some studies have demonstrated that subjects with cardiometabolic diseases present reduced baseline levels of $CD34^+/VEGFR2^+$ cells [11] when compared with healthy controls. However, the current population with MetS is free of overt disease or pharmacological treatment, and these factors are known to alter the results [12, 13, 44].

In conclusion, despite being free of established chronic diseases and pharmacological treatment, the subjects with MetS already presented an early impairment of endothelial function, as shown by increased baseline levels of sE-selectin, sICAM-1, and MMP-9. In addition, subjects with early MetS already exhibited an impaired response to exercise in terms of CACs and MMP-9 activity. The analysis of these biomarker changes could be potentially useful to develop preventive measures before the onset of MetS-related diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors would like to thank Helena Naly Miguens Rocha for technical assistance and Tyler Bammert, Collin Beckstrom, and Grace Lincenberg for their English review of the paper. This work was supported by the State of Rio de Janeiro Agency for Research (FAPERJ, E-26/102.378/2009) and the National Council of Scientific and Technological Development (CNPq, 307251/2009-8).

References

[1] World Health Organization, *Cardiovascular Diseases*, World Health Organization, Geneva, Switzerland, 2014, http://www.who.int.

[2] H.-M. Lakka, D. E. Laaksonen, T. A. Lakka et al., "The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men," *Journal of the American Medical Association*, vol. 288, no. 21, pp. 2709–2716, 2002.

[3] K. G. M. M. Alberti, R. H. Eckel, S. M. Grundy et al., "Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity," *Circulation*, vol. 120, no. 16, pp. 1640–1645, 2009.

[4] A. Nikolopoulou and N. P. E. Kadoglou, "Obesity and metabolic syndrome as related to cardiovascular disease," *Expert Review of Cardiovascular Therapy*, vol. 10, no. 7, pp. 933–939, 2012.

[5] L. M. Stoolman, "Adhesion molecules involved in leukocyte recruitment and lymphocyte recirculation," *Chest*, vol. 103, supplement 2, no. 2, pp. 79S–86S, 1993.

[6] X. Chen and T. O. Scholl, "Maternal biomarkers of endothelial dysfunction and preterm delivery," *PLoS ONE*, vol. 9, no. 1, Article ID e85716, 2014.

[7] L. Gómez Rosso, M. B. Benítez, M. C. Fornari et al., "Alterations in cell adhesion molecules and other biomarkers of cardiovascular disease in patients with metabolic syndrome," *Atherosclerosis*, vol. 199, no. 2, pp. 415–423, 2008.

[8] T. Fernandes, J. S. Nakamuta, F. C. Magalhães et al., "Exercise training restores the endothelial progenitor cells number and

function in hypertension: implications for angiogenesis," *Journal of Hypertension*, vol. 30, no. 11, pp. 2133–2143, 2012.

[9] V. Spigoni, A. Picconi, M. Cito et al., "Pioglitazone improves in vitro viability and function of endothelial progenitor cells from individuals with impaired glucose tolerance," *PLoS ONE*, vol. 7, no. 11, Article ID e48283, 2012.

[10] F. Rossi, C. Bertone, F. Montanile et al., "HDL cholesterol is a strong determinant of endothelial progenitor cells in hypercholesterolemic subjects," *Microvascular Research*, vol. 80, no. 2, pp. 274–279, 2010.

[11] I. Jialal, S. Devaraj, U. Singh, and B. A. Huet, "Decreased number and impaired functionality of endothelial progenitor cells in subjects with metabolic syndrome: implications for increased cardiovascular risk," *Atherosclerosis*, vol. 211, no. 1, pp. 297–302, 2010.

[12] J.-Y. Sun, L. Zhai, Q.-L. Li et al., "Effects of ACE inhibition on endothelial progenitor cell mobilization and prognosis after acute myocardial infarction in type 2 diabetic patients," *Clinics*, vol. 68, no. 5, pp. 665–673, 2013.

[13] S. Dimmeler, A. Aicher, M. Vasa et al., "HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway," *Journal of Clinical Investigation*, vol. 108, no. 3, pp. 391–397, 2001.

[14] M. Hamer and A. Steptoe, "Vascular inflammation and blood pressure response to acute exercise," *European Journal of Applied Physiology*, vol. 112, no. 6, pp. 2375–2379, 2012.

[15] E. Rullman, K. Olsson, D. Wågsäter, and T. Gustafsson, "Circulating MMP-9 during exercise in humans," *European Journal of Applied Physiology*, vol. 113, no. 5, pp. 1249–1255, 2013.

[16] P. Ferroni, S. Basili, F. Martini et al., "Serum metalloproteinase 9 levels in patients with coronary artery disease: a novel marker of inflammation," *Journal of Investigative Medicine*, vol. 51, no. 5, pp. 295–300, 2003.

[17] J. L. Rummens, A. Daniëls, P. Dendale et al., "Suppressed increase in blood endothelial progenitor cell content as result of single exhaustive exercise bout in male revascularised coronary artery disease patients," *Acta Clinica Belgica*, vol. 67, no. 4, pp. 262–269, 2012.

[18] D. R. Matthews, J. P. Hosker, A. S. Rudenski, B. A. Naylor, D. F. Treacher, and R. C. Turner, "Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man," *Diabetologia*, vol. 28, no. 7, pp. 412–419, 1985.

[19] K. Skogstrand, P. Thorsen, B. Nørgaard-Pedersen, D. E. Schendel, L. C. Sørensen, and D. M. Hougaard, "Simultaneous measurement of 25 inflammatory markers and neurotrophins in neonatal dried blood spots by immunoassay with xMAP technology," *Clinical Chemistry*, vol. 51, no. 10, pp. 1854–1866, 2005.

[20] R. T. Carson and D. A. A. Vignali, "Simultaneous quantitation of 15 cytokines using a multiplexed flow cytometric assay," *Journal of Immunological Methods*, vol. 227, no. 1-2, pp. 41–52, 1999.

[21] O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, "Protein measurement with the Folin phenol reagent," *The Journal of Biological Chemistry*, vol. 193, no. 1, pp. 265–275, 1951.

[22] M. J. Davies, J. L. Gordon, A. J. H. Gearing et al., "The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis," *Journal of Pathology*, vol. 171, no. 3, pp. 223–229, 1993.

[23] S.-J. Hwang, C. M. Ballantyne, A. R. Sharrett et al., "Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study," *Circulation*, vol. 96, no. 12, pp. 4219–4225, 1997.

[24] I. A. Fernandes, A. R. K. Sales, N. G. Rocha, B. M. Silva, L. C. Vianna, and A. C. L. Da Nóbrega, "Preserved flow-mediated dilation but delayed time-to-peak diameter in individuals with metabolic syndrome," *Clinical Physiology and Functional Imaging*, vol. 34, no. 4, pp. 270–276, 2014.

[25] M. H. Tayebjee, S. K. Nadar, R. J. MacFadyen, and G. Y. H. Lip, "Tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9 levels in patients with hypertension: relationship to tissue Doppler indices of diastolic relaxation," *American Journal of Hypertension*, vol. 17, no. 9, pp. 770–774, 2004.

[26] J. Sundström and R. S. Vasan, "Circulating biomarkers of extracellular matrix remodeling and risk of atherosclerotic events," *Current Opinion in Lipidology*, vol. 17, no. 1, pp. 45–53, 2006.

[27] F. Zaldivar, J. Wang-Rodriguez, D. Nemet et al., "Constitutive pro- and anti-inflammatory cytokine and growth factor response to exercise in leukocytes," *Journal of Applied Physiology*, vol. 100, no. 4, pp. 1134–1141, 2006.

[28] M. Balan and M. Locke, "Acute exercise activates myocardial nuclear factor kappa B," *Cell Stress and Chaperones*, vol. 16, no. 1, pp. 105–111, 2011.

[29] G. C. Bogdanis, P. Stavrinou, I. G. Fatouros et al., "Short-term high-intensity interval exercise training attenuates oxidative stress responses and improves antioxidant status in healthy humans," *Food and Chemical Toxicology*, vol. 61, pp. 171–177, 2013.

[30] J. Lara Fernandes, C. V. Serrano Jr., F. Toledo et al., "Acute and chronic effects of exercise on inflammatory markers and B-type natriuretic peptide in patients with coronary artery disease," *Clinical Research in Cardiology*, vol. 100, no. 1, pp. 77–84, 2011.

[31] A. C. L. da Nobrega, "The subacute effects of exercise: concept, characteristics, and clinical implications," *Exercise and Sport Sciences Reviews*, vol. 33, no. 2, pp. 84–87, 2005.

[32] D. J. Green, G. O'Driscoll, M. J. Joyner, and N. T. Cable, "Exercise and cardiovascular risk reduction: time to update the rationale for exercise?" *Journal of Applied Physiology*, vol. 105, no. 2, pp. 766–768, 2008.

[33] K. Sonnenschein, T. Horváth, M. Mueller et al., "Exercise training improves in vivo endothelial repair capacity of early endothelial progenitor cells in subjects with metabolic syndrome," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 18, no. 3, pp. 406–414, 2011.

[34] J. M. Fernández, D. Rosado-Álvarez, M. E. D. S. Grigoletto et al., "Moderate-to-high-intensity training and a hypocaloric Mediterranean diet enhance endothelial progenitor cells and fitness in subjects with the metabolic syndrome," *Clinical Science*, vol. 123, no. 6, pp. 361–373, 2012.

[35] M. Teraa, R. W. Sprengers, P. E. Westerweel et al., "Bone marrow alterations and lower endothelial progenitor cell numbers in critical limb ischemia patients," *PLoS ONE*, vol. 8, no. 1, Article ID e55592, 2013.

[36] E. Chang, J. Paterno, D. Duscher et al., "Exercise induces stromal cell-derived factor-1alpha-mediated release of endothelial progenitor cells with increased vasculogenic function," *Plastic and Reconstructive Surgery*, vol. 135, no. 2, pp. 340e–350e, 2015.

[37] K. Kruger, R. Klocke, J. Kloster, S. Nikol, J. Waltenberger, and F. C. Mooren, "Activity of daily living is associated with circulating

$CD34^+/KDR^+$ cells and granulocyte colony-stimulating factor levels in patients after myocardial infarction," *Journal of Applied Physiology*, vol. 116, no. 5, pp. 532–537, 2014.

[38] V. Furmento, J. Marino, V. Blank, and L. Roguin, "The granulocyte colony-stimulating factor (G-CSF) upregulates metalloproteinase-2 and VEGF through PI3K/Akt and Erk1/2 activation in human trophoblast Swan 71 cells," *Placenta*, vol. 35, no. 11, pp. 937–946, 2014.

[39] A. C. Newby, "Metalloproteinase expression in monocytes and macrophages and its relationship to atherosclerotic plaque instability," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 12, pp. 2108–2114, 2008.

[40] A. Cicero, G. Derosa, M. Manca, M. Bove, C. Borghi, and A. Gaddi, "Vascular remodeling and prothrombotic markers in subjects affected by familial combined hyperlipidemia and/or metabolic syndrome in primary prevention for cardiovascular disease," *Endothelium*, vol. 14, no. 4-5, pp. 193–198, 2007.

[41] B. Heissig, K. Hattori, S. Dias et al., "Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of Kit-ligand," *Cell*, vol. 109, no. 5, pp. 625–637, 2002.

[42] S. Furukawa, T. Fujita, M. Shimabukuro et al., "Increased oxidative stress in obesity and its impact on metabolic syndrome," *The Journal of Clinical Investigation*, vol. 114, no. 12, pp. 1752–1761, 2004.

[43] N. Werner, S. Kosiol, T. Schiegl et al., "Circulating endothelial progenitor cells and cardiovascular outcomes," *The New England Journal of Medicine*, vol. 353, no. 10, pp. 999–1007, 2005.

[44] C. Endtmann, T. Ebrahimian, T. Czech et al., "Angiotensin II impairs endothelial progenitor cell number and function in vitro and in vivo: implications for vascular regeneration," *Hypertension*, vol. 58, no. 3, pp. 394–403, 2011.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 394183, 10 pages
http://dx.doi.org/10.1155/2015/394183

Review Article

Cardiovascular Reflexes Activity and Their Interaction during Exercise

Antonio Crisafulli,[1] Elisabetta Marongiu,[1] and Shigehiko Ogoh[2]

[1]*Department of Medical Sciences, Sports Physiology Lab, University of Cagliari, Via Porcell 4, 09124 Cagliari, Italy*
[2]*Department of Biomedical Engineering, Toyo University, 2100 Kujirai, Kawagoe-shi, Saitama 350-8585, Japan*

Correspondence should be addressed to Antonio Crisafulli; crisafulli@tiscali.it

Received 9 May 2015; Revised 26 July 2015; Accepted 28 July 2015

Academic Editor: Kimimasa Tobita

Cardiac output and arterial blood pressure increase during dynamic exercise notwithstanding the exercise-induced vasodilation due to functional sympatholysis. These cardiovascular adjustments are regulated in part by neural reflexes which operate to guarantee adequate oxygen supply and by-products washout of the exercising muscles. Moreover, they maintain adequate perfusion of the vital organs and prevent excessive increments in blood pressure. In this review, we briefly summarize neural reflexes operating during dynamic exercise with particular emphasis on their interaction.

1. Hemodynamic Regulation during Dynamic Exercise: General Review and Functions

Physical activities with large muscle mass, such as running, cycling, and rowing, can produce a reduction in systemic vascular resistance (SVR) because of the intense metabolic vasodilatation in the muscle vasculature via functional sympatholysis [1, 2]. This fact constitutes a challenge for the cardiovascular apparatus and it would cause a drop in blood pressure if control mechanisms did not contemporarily augment cardiac output (CO). Thus, the active muscle competes with blood pressure regulation for blood flow. Despite the vasodilation-induced SVR decrease, dynamic exercise in normal subjects is characterized only by a small to moderate increase in mean arterial pressure (MAP) [3–5]. Convincing evidence demonstrates that this fine hemodynamic tuning is determined by the activity of neural mechanisms which control the cardiovascular system and regulate circulation to guarantee adequate oxygen supply and washout of metabolic end-products to exercising muscles. These mechanisms also regulate arterial blood pressure, so that perfusion of the vital organs is reached and blood pressure does not vary excessively.

There are at least three neural mechanisms participating in this cardiovascular regulation: (1) the exercise pressor reflex, (2) the central command, and (3) the arterial baroreflex.

The *medulla* contains the major nuclei that control blood pressure and the cardiovascular system. These nervous circuits are extensively reviewed in other excellent papers [6, 7]. It is believed that the "central command" sets a basal level of sympathetic activity and vagal withdrawal closely related to the intensity of the strain and to motor drive from the motor cortex [8–12]. In this neural mechanism, the cardiovascular control areas located in the medulla are activated by regions of the brain responsible for motor unit recruitment. This basic level of autonomic activation is then modulated by the exercise pressor reflex, which originates from peripheral signals arising from mechano- and metaboreceptors (types III and IV nerve endings within the muscle) that reflexively modulate sympathetic activity taking into account the mechanical and metabolic conditions in the working muscle [12–16]. In detail, it is known that groups III and IV nerve endings excite neurons in the nucleus of the solitary tract (NST) in the medulla. A subset of the NTS neurons activated by these afferents is thought to directly excite neurons of the ventrolateral medulla, which are the primary output for sympathetic activity [6, 7]. This autonomic modulation originating from the central command and the exercise pressor reflex increases HR and enhances myocardial contractility, which together

concur in raising CO. Sympathetic stimulation is in turn modulated by baroreflexes, which oppose any mismatch between vascular resistance and CO by controlling muscle vasodilatation and cardiac chronotropism in order to avoid excessive variation in blood pressure [17–19].

Thus, dynamic exercise elicits marked cardiovascular and autonomic adjustments which include increases in CO, MAP, and SVR reduction. This hemodynamic status is regulated by the nervous system by the integration of information coming from the motor cortex (central command), from muscle receptors (exercise pressor reflex), and from receptors in the aortic, carotid, heart, and pulmonary arteries (arterial and cardiopulmonary baroreflexes).

One key point of the functioning of these reflexes is how they interact during dynamic exercise. There is some redundancy between them and neural occlusion can be operative. Moreover, from several observations it appears that both the central command and the exercise pressor reflex can modulate the activity of the baroreflex [19]. In this review, we will briefly summarize the activities of these neural reflexes with particular emphasis on their integration during dynamic exercise.

2. Exercise Pressor Reflex

Since the seminal research by Alam and Smirk [20, 21] a great bulk of evidence has demonstrated that metabolic reflex coming from skeletal muscle evokes cardiovascular adjustments during exercise. Subsequently, Coote et al. [22] demonstrated that the muscle pressor reflex could be elicited by ventral root stimulation. Then, McCloskey and Mitchell [8] showed the involvement of group III/IV afferents in this cardiovascular reflex. This reflex is known as the muscle "metaboreflex." It was later demonstrated that mechanical changes in muscles and tendons can also elicit cardiovascular responses [23]. This reflex has been termed "mechanoreflex." These two reflexes of muscular origin together constitute the exercise pressor reflex.

It is well established that these two reflexes have their afferent arm in groups III and IV nerve endings within the muscle, with type III nerve afferents mainly acting as mechanoreceptors and type IV as metaboreceptors [24]. It is however important to underline that this classification is not imperative and that both fiber types can act dually as metabo- and mechanoreceptors. Moreover, evidence suggests that mechanoreceptors can be sensitized by metabolites accumulation [25] thereby rendering the specific contribution of mechano- and metaboreceptors to the exercise pressor reflex difficult to evaluate during exercise. These receptors collect information concerning the mechanical and metabolic conditions of contracting muscles and send this piece of information to cardiovascular controlling centers located in the *medulla*, where the information is integrated and elaborated. Then, cardiovascular medullary centers organize the hemodynamic response to exercise taking into account the mechanical and metabolic status of the working muscle [10, 26, 27].

Several substances have been demonstrated to be able to activate the metaboreflex, such as lactic acid, potassium, bradykinin, arachidonic acid products, ATP, deprotonated phosphate, and adenosine [2], whereas the role played by reactive oxygen species is controversial [28]. Moreover, studies with ^{31}P nuclear magnetic resonance spectroscopy revealed that the metaboreflex can be activated by decrements in intramuscular pH [29, 30]. These findings are interpreted with the concept that the metaboreflex is activated whenever blood flow to contracting muscles is insufficient to warrant oxygen delivery and/or metabolites washout [13, 31], thereby suggesting that this reflex corrects any possible mismatch between blood flow and metabolism in the muscle. However, there is evidence that in humans the metaboreflex can be active even during mild exercise, when there is sufficient O_2 delivery to the muscle. In this situation there is no evident mismatch between muscle flow and metabolism, thereby demonstrating the essential role of the metaboreflex in the normal blood pressure response even for light exercise intensities [9]. Therefore, the metaboreflex might be responsible for a tonically active feedback to the cardiovascular control areas which induce cardiovascular changes whenever the muscle metabolism is activated by muscle contractions, even at mild intensities of effort [15, 32, 33].

From a hemodynamic point of view, the typical consequence of metaboreflex recruitment is an increase in MAP [10, 13, 15]. This response is reached by modulating both SVR and CO. However, whilst SVR increase due to sympathetic vasoconstriction is a well-described phenomenon [13, 15, 34], the consequences upon central hemodynamics and CO are less studied and characterized. It is well ascertained that the effect on HR is limited or absent, since studies using the postexercise muscle ischemia method often report very mild or null effects on this parameter [13, 15, 34–39]. However, if the metaboreflex is evoked during exercise by causing muscle ischemia an HR response is evident [40]. The reason for such HR behavior is explained in detail in the *reflex interaction during exercise* paragraph.

In healthy individuals, the metaboreflex can also influence cardiac contractility, preload, and stroke volume (SV) as suggested by recent and past evidence [15, 16, 33, 36, 38, 40–47]. The possibility to recruit the functional reserve of preload and contractility appears crucial since impairment in one or both parameters causes abnormal cardiovascular adjustments to exercise, as observed in situations such as heart failure, spinal cord injured patients, and subjects with diastolic dysfunction [36, 43, 48]. Of note, it has been reported that metaboreflex can induce venoconstriction and splanchnic vasoconstriction, thereby increasing ventricular filling pressure. This phenomenon facilitates venous return and produces a sort of blood volume "centralization" in order to support SV and CO [36, 41, 49]. In particular, a reduction in ventricular filling rate, a measure of diastolic function, has been reported to impair the metaboreflex-induced SV response [36, 38, 49, 50]. Moreover, it has been recently reported that healthy, elderly subjects show an impaired SV response via the metaboreflex as compared to young individuals because of their reduction in cardiac compliance which impaired diastolic filling [43]. Therefore, these results suggest that diastolic capacity is important to achieve a normal hemodynamic response during the metaboreflex.

Thus, the available literature suggests that the hemodynamic response to metaboreflex activation is a highly integrated phenomenon. A complex interplay between HR, cardiac performance, preload, and afterload occurs to achieve, at least in healthy individuals, the normal cardiovascular response to exercise [13, 14, 33, 51].

As concerns the mechanical branch of the exercise pressor reflex, it has been reported that the mechanoreflex can also trigger cardiovascular reflex. Actually, mechanical distortion of type III nerve endings in contracting muscles may substantially increase blood pressure [52, 53]. The mechanoreflex activation has been reported to inhibit cardiac vagal tone which, in turn, causes a rapid and sustained elevation in HR at the beginning of exercise [23]. It should however be kept in mind that, in humans, the mechanoreflex is more difficult to isolate than metaboreflex as muscle contractions, which are needed to recruit the mechanoreflex, are accompanied by both central command and metaboreflex activation, thus rendering the isolation of mechanoreflex from the other two reflexes difficult to achieve. Furthermore, as previously stated, mechanoreceptors can be sensitized by the accumulation of metabolites, which renders the metaboreflex and mechanoreflex contribution difficult to isolate during exercise. For these reasons, research on the mechanoreflex is less abundant than that on metaboreflex and a clear and complete picture of the hemodynamic consequences of pure mechanoreflex activation is lacking. Further studies are warranted to better clarify the role of mechanoreflex in the cardiovascular adjustment to exercise pressor reflex activation.

In summary, from available data it seems that the exercise pressor reflex can adjust all four hemodynamic modulators (i.e., chronotropism, inotropism, cardiac preload, and afterload) to reach the target blood pressure during exercise. However, while the metaboreflex contribution to this reflex is well characterized, less is known about the hemodynamic effects of mechanoreflex activation.

3. Central Command

The Nobel Prize winning Krogh and his colleague Lindhard [54] in their early seminal work were the first to propose the concept that the motor cortex could influence the cardiovascular and ventilatory apparatus during exercise. Then, the term "central command" was introduced and it was defined as a "feed-forward mechanism involving parallel activation of motor and cardiovascular centers" [55]. Coherently with the definition, this nervous mechanism does not require any feedback from peripheral muscle. Rather, the central command and the exercise pressor reflex operate in parallel to augment the sympathetic tone during exercise. However, it should be underscored that while central command activation leads to both sympathoactivation and vagal withdrawal [56, 57], this latter effect still has to be demonstrated for the exercise pressor reflex.

It has been demonstrated that central command consists of neural impulses from the motor cortex that irradiate to autonomic neurons in the brain stem and that its activation establishes, at the onset of exercise, a basal level of sympathetic and parasympathetic efferent activity closely linked to the intensity of the exercise performed. Then, this basic autonomic activity is further modulated by the activation of the exercise pressor reflex [8–10, 16]. However, the precise cortical site subserving this mechanism remains unclear. While regions of the higher brain participating in central command activity have been consistently identified (i.e., premotor areas and supplementary motor areas) [58], other brain areas are likely involved in the phenomenon. In particular, studies with neuroimaging and using brain stimulation during surgery have documented that other regions of the brain participate in the cardiovascular regulation during exercise. In detail, cerebellum, insula, anterior cingulate cortex, medial prefrontal cortex, hippocampus, thalamus, and possibly others have all been demonstrated to be potentially involved in this mechanism and all may take part in the circulatory adjustments to exercise [11, 58–63]. Moreover, in recent investigations a key role for the periaqueductal grey (PAG) in the neurocircuitry of central command has been demonstrated, in particular for the lateral and the dorsal lateral PAG. This substance is a functional interface between the forebrain and lower brainstem and it is activated during exercise [59, 63]. In a recent extensive review it has been proposed that PAG fulfils many requirements of a central command center [64].

Whilst it has been demonstrated that exercise pressor reflex activation can regulate the main hemodynamic modulators (i.e., heart rate, cardiac contractility, preload, and afterload; see the *exercise pressor reflex* paragraph), fewer studies have been conducted on the hemodynamic consequences of central command activation, as most of them focused on HR, blood pressure responses, and sympathetic-parasympathetic balance, while less attention has been put on central hemodynamics. It is well ascertained that central command can increase HR and blood pressure by increasing sympathetic and decreasing parasympathetic tone, respectively; however, there are no investigations demonstrating any effect of central command on cardiac contractility, preload, or afterload. This is also because it is difficult to isolate the hemodynamic adjustments due central command activity from those arising from exercise pressor reflex. Further research is warranted to better characterize this topic.

Summing up, central command is a feed-forward mechanism originating from several regions of the brain which modulate autonomic functions on the basis of the motor cortex activation. The typical consequence of its activation is an increase in HR and blood pressure which occurs rapidly at the beginning of exercise.

4. Baroreflex

Arterial baroreceptors are located at the medial-adventitial border of blood vessels in the carotid sinus bifurcation and aortic arch. They are pivotal in inducing the rapid adjustments that occur during acute cardiovascular stress via control over HR and peripheral vascular responses to changes in arterial pressure [65, 66]. When arterial blood pressure is elevated or reduced acutely, the baroreceptors are stretched or compressed and this deformation of baroreceptors leads to an

increase or decrease in afferent neuronal firing, respectively. These afferent neural responses via baroreceptors result in reflex-mediated systemic neural adjustments with changes in sympathetic and parasympathetic nerve activities, which affect both central (cardiac) and peripheral (vessels) circulation in order to return arterial blood pressure to its original operating pressure point.

4.1. Blood Pressure Regulation during Exercise. Since the 1960s, the effect of exercise on the arterial baroreflex function has been reported by many investigators [67–70]. In particular, in earlier studies some investigators questioned the functional role of the arterial baroreflex during exercise [19, 71, 72]. It was believed that the directionally analogous response of HR and arterial blood pressure (increase) to dynamic exercise suggested that the baroreflex was altered or inhibited because the baroreflex-mediated HR responses should be the opposite to change in arterial blood pressure as a negative feedback control system. Therefore, early research suggested that the arterial baroreflex was "switched off" as it was unnecessary for the cardiovascular adjustments to exercise or alternatively that the sensitivity of the reflex was significantly decreased during exercise to increase both HR and arterial blood pressure [19, 70, 72]. Indeed, Iellamo et al. [73, 74] reported that the sensitivity of the cardiac-arterial baroreflex is gradually attenuated from rest to heavy dynamic exercise. Potts et al. [75] were the first to report in humans studies that the full baroreflex stimulus-response curve was well preserved without its maximal sensitivity during increasing exercise workload. These findings suggest that the carotid baroreflex is reset during dynamic exercise and it functionally operates around the exercise-induced increase in arterial blood pressure. Ogoh et al. [76] investigated the physiological mechanism of exercise-induced resetting of carotid baroreflex by using the blockade of sympathetic or parasympathetic nerve activity. In their study, the authors demonstrated that the operating point of the cardiac carotid baroreflex was progressively shifted and relocated in order to regulate the prevailing arterial pressure by vagal withdrawal with reduced sensitivity as compared to its maximum. These inconsistent results are associated with the different methods of analysis. The dynamic analysis of the previous studies (i.e., sequence technique and transfer function analysis) shows only the part of baroreflex function, for example, the baroreflex sensitivity at the operating point but does not allow the determination of the full baroreflex stimulus-response curve in the transition from rest to mild, moderate, and heavy exercise workloads [74, 76]. The upward and rightward shift of the stimulus-response curve to the higher arterial blood pressure and HR allows the baroreflex to operate at the prevailing arterial blood pressure during exercise as effectively as operating at rest, and it also preserves the reflex gain [19, 66, 72, 77]. Further information arises from additional studies showing that this resetting occurs in direct relation to the intensity of effort, without a change in sensitivity [75, 76, 78–80]. Nowadays, exercise-induced "resetting" of the baroreflex function has been well established.

4.2. Why Is Baroreflex Resetting Important? The "resetting" of the arterial baroreflex is essential to evoke and maintain an effective autonomic nervous system modulation and an adequate cardiovascular adjustment to exercise. In exercising dogs, acute denervation of baroreceptors leads to overnormal increase in arterial blood pressure [81]. Similar findings have been reported in humans with surgically denervated carotid baroreceptors. In these subjects, the arterial blood pressure response to exercise is higher than in normal individuals [82, 83]. In addition, when baroreflex activation was counteracted by pharmacologically clamping blood pressure at resting values and preventing the normal exercise-induced increase in arterial blood pressure, a threefold increase in sympathetic nerve activity during handgrip exercise was observed, compared with a control exercise condition [84]. These findings provide proof that the baroreflex acts to finely balance the opposing effects of sympathetic vasoconstriction and metabolic vasodilation, and it also acts to partly restrain the arterial blood pressure response to exercise by buffering activation of the increase in sympathetic activity due to the central command and the exercise pressor reflex.

In other words, if baroreflex function is impaired, then there is an insufficient buffering of the sympathetic tone during exercise. This fact would lead to augmented vasoconstriction and it would lead to a larger increase in blood pressure [19]. Moreover, it might also cause a reduction in muscle blood flow and induce muscle ischemia, thereby contributing to reductions in exercise tolerance [71].

4.3. Functional Sympatholysis and Baroreflex. It has been consistently demonstrated that the full expression of sympathetic activation is metabolically inhibited within exercising tissue [85–91]. This phenomenon has been termed "functional sympatholysis." This metabolic-induced restraint of sympathetic vasoconstriction is also related to the intensity of the effort, as it becomes more evident at harder strains [91–93]. It has been reported that mechanisms for functional sympatholysis are associated with the production of several metabolites, such as nitric oxide [88, 94, 95], adenosine, and prostacyclin [96–98] as well as increases in muscle temperature [99], hypoxia [100], and metabolic acidosis [101]. Interestingly, baroreflex control of blood pressure is well maintained from rest to heavy exercise notwithstanding the attenuation of local vascular response to sympathetic activation in the active muscle. Previously, Keller et al. [102] examined the importance of baroreflex-mediated changes in leg vascular conductance of exercising and nonexercising tissue in the regulation of arterial blood pressure during one-legged knee extension exercise in humans. In this study, carotid baroreflex-mediated reduction in leg vascular conductance to the sympathoexcitation was attenuated in the exercising leg compared with resting condition or the nonexercising leg. This finding indicates the presence of a modulation of sympathetically mediated alterations in leg vascular conductance within the active muscle during exercise. However, despite the attenuation in sympathetic responsiveness (i.e., functional sympatholysis) in the exercising leg, the gains between percentage changes in muscle sympathetic nerve activity and

absolute changes in leg vascular conductance were not different in the exercising leg. Importantly, a 3- to 4-fold increase in steady-state leg vascular conductance occurred during exercise in the exercising leg. Therefore, a balance must exist between baroreflex-mediated changes in conductance of a given vascular bed and the influence of exercise-induced attenuation of sympathetic vasoconstriction. Probably, this balance permits a continuous increase in perfusion of the exercising muscle together with a conserved ability of the baroreflex to control vascular conductance which, ultimately, allows maintaining blood pressure during exercise [102]. More importantly, changes in vasomotor, rather than in HR, are the primary targets of the arterial baroreflex in order to regulate arterial blood pressure during mild to heavy dynamic exercise despite a functional sympatholysis [76].

5. Reflexes Interaction during Exercise

During exercise, exercise pressor reflex, central command, and baroreflex are all activated and complex interaction occurs between these reflexes. While it is well ascertained that some redundancy and neural occlusion exist between exercise pressor reflex and central command (i.e., their effects do not sum), it is also remarkable that they can all modulate the activity of the other two. The most studied interaction is probably the modulation of baroreflex operated by central command and exercise pressor reflex. In 1990 Rowell and O'Leary [10] proposed a hypothetical scheme of the roles of central command and the exercise pressor reflex in the resetting of the baroreflex during exercise. Subsequently, Raven and colleagues confirmed in a series of experiments this original hypothesis [19, 66, 72, 78]. Thus, it is now well established that both central command and the exercise pressor reflex are involved in the mechanism of baroreflex resetting during exercise. Previous studies that used the vibration technique [103], electrical muscle stimulation [73, 104], partial axillary blockade [105], and partial neuromuscular blockade [106] to manipulate central command in humans demonstrated that selective increase in central command activity relocates the carotid baroreflex stimulus-response curve for both MAP and HR rightward to higher arterial pressures and upward on the response arm without changes in sensitivity. In addition, postexercise muscle ischemia [107], lower positive pressure [108, 109], and medical antishock [110] were used to identify the role of the exercise pressure reflex in exercise-induced baroreflex resetting. An enhanced activation of the exercise pressor reflex relocated the carotid-mean arterial pressure stimulus-response curve upward on the response arm and rightward to higher arterial pressures. However, the exercise pressor reflex only resets the carotid—cardiac stimulus—response curve rightward to operate at higher arterial pressures with no upward resetting. Collectively, these previous investigations identified that both central command and the exercise pressor reflex might reset baroreflex during exercise.

Gallagher et al. [111] assessed the interactive relationship between central command and the exercise pressor reflex for the exercise-induced resetting of carotid baroreflex. In this study, central command and exercise pressure reflex were manipulated by using neuromuscular blockade (vecuronium) and antishock trousers, respectively. Interestingly, exercise-induced baroreflex resetting was greater during the combined enhanced activation of central command and the exercise pressor reflex than during overactivation of either input alone. This finding suggests that central command and the exercise pressor reflex interact. As a consequence, signals from one input facilitate signals from the other, resulting in an accentuated resetting of the baroreflex during exercise. Central command, as a feed-forward mechanism, is likely to be the primary regulator of exercise-induced baroreflex resetting, whereas the exercise pressor reflex operates mainly as a feed-back mechanism. Thus, it exerts a more modulatory role. Furthermore, it seems that both inputs interact and are important for the complete exercise-induced baroreflex resetting [66].

The interaction between reflexes clearly appears during postexercise muscle ischemia (PEMI), a method usually employed to study the cardiovascular effects of metaboreflex activation [15, 33]. During PEMI, there is normally no HR response notwithstanding the activation of exercise pressor reflex and the augmented sympathetic activity. The absence of HR response in this setting is the consequence of the fact that the rise of sympathetic activity due to metaboreflex activation is counteracted by the concomitantly augmented parasympathetic outflow due to the central command deactivation and the concomitant enhanced arterial baroreflex activity that buffers the metaboreflex-mediated increase in MAP [14, 17, 40, 112]. Thus, if the metaboreflex is activated by the PEMI method, the elevated sympathetic activity to sinus node is counteracted by enhanced parasympathetic tone due to the withdrawal of central command and to the sympathetic-buffering effect of baroreflex activation. This fact is not evident when metaboreflex is activated during exercise when central command is operating [40], thereby indicating that central command acts as a modulator of baroreflex activity during exercise.

Along with central command and exercise pressor reflex, cardiopulmonary baroreflex can also modulate arterial baroreflex during exercise. Cardiopulmonary baroreflex plays a pivotal role in maintaining the exercise-induced increase in blood pressure [113, 114]. Moreover, several studies have shown the interaction between carotid and cardiopulmonary baroreflexes. They indicated that unloading of the cardiopulmonary baroreceptors enhanced maximal gain of carotid baroreflex function at rest and during exercise [109, 115–119]. Interestingly, alteration in cardiopulmonary baroreceptor load during dynamic exercise affects not only the prevailing exercise-induced arterial blood pressure, but also the resetting of the arterial baroreflex [120–122].

Ogoh et al. [122] increased central blood volume (cardiopulmonary baroreceptor load) by increasing pedal frequency to enhance the muscle pump at the same amount of central command. Then, they demonstrated that the magnitude of exercise-induced increases in arterial blood pressure was reduced and carotid baroreflex reset leftward and downward during dynamic exercise. Moreover, Volianitis et al. [120] reported that when leg cycling was added to

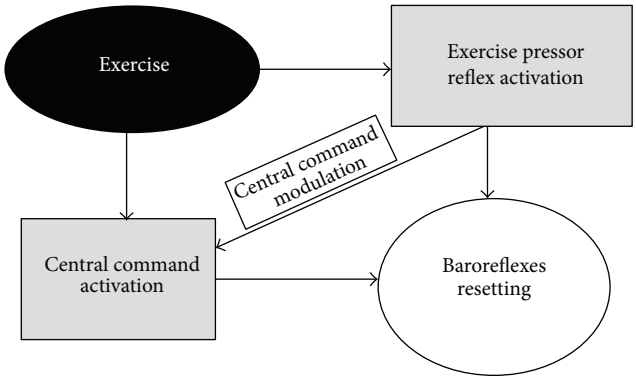


Figure 1: Interactions between the three main neural reflexes operating during exercise. See text for more details.

arm-cranking exercise, arterial blood pressure was reduced below that of arm exercise alone and resulted in relocation of the operating point of the carotid baroreflex-MAP curve to the lower arterial blood pressure despite greater activation of central command and the exercise pressor reflex. These findings suggest that input from cardiopulmonary baroreceptors can influence arterial baroreflex control during exercise. In particular, cardiopulmonary baroreflex is associated with the locus of the operating point of the baroreflex-mean arterial pressure curve. Collectively, the cardiopulmonary baroreflex also resets during physical activity to operate around the exercise-induced increase in central blood volume without a change in reflex sensitivity [123]. Therefore, these results indicate that the cardiopulmonary baroreflex plays an important role in baroreflex resetting during exercise and it operates together with central command and the exercise pressor reflex.

Interaction has also been demonstrated between central command and the exercise pressor reflex. Indeed, some evidence suggests that input from types III and IV muscle afference modulates the central command activity and exerts an inhibitory effect on central motor drive. Furthermore, these signals may influence the perception of effort [124]. In detail, it has been demonstrated that attenuation of somatosensory signals from the muscle obtained with epidural anesthesia, which reduced afferent input, resulted in an increase in central command activity. However, HR and blood pressure responses were attenuated as compared to a normal exercise, thereby suggesting that afferent feedback from the muscle is essential in normal cardiovascular adjustments to exercise [9, 124, 125]. Therefore, it seems that central command cannot work properly without adequate feedback from peripheral muscle and that, at the same time, this feedback limits central command and motor drive. However, this is quite a complex issue and further research is warranted to better clarify the complex interaction between central command and exercise pressor reflex.

Figure 1 depicts the various interactions between reflexes which are supposed to be operative during exercise.

6. Conclusions

In summary, cardiovascular regulation during exercise is reached through the contemporary integration and interaction between input arising from motor cortex, skeletal muscle receptors, and arterial baroreceptors. While it is well ascertained that baroreflex activity is modulated by both central command and exercise pressor reflex, less is known about the interaction between central command and exercise pressor reflex. Further research in this field is warranted.

Conflict of Interests

The authors have no conflict of interests directly relevant to the content of this paper.

Acknowledgment

The authors wish to thank Mr. Barry Mark Wheaton for his editorial assistance.

References

[1] M. Ichinose, S. Maeda, N. Kondo, and T. Nishiyasu, "Blood pressure regulation II: what happens when one system must serve two masters—oxygen delivery and pressure regulation?" *European Journal of Applied Physiology*, vol. 114, no. 3, pp. 451–465, 2014.

[2] M. N. Murphy, M. Mizuno, J. H. Mitchell, and S. A. Smith, "Cardiovascular regulation by skeletal muscle reflexes in health and disease," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 301, no. 4, pp. H1191–H1204, 2011.

[3] S. F. Lewis, W. F. Taylor, R. M. Graham, W. A. Pettinger, J. E. Schutte, and C. G. Blomqvist, "Cardiovascular responses to exercise as functions of absolute and relative work load," *Journal of Applied Physiology: Respiratory Environmental and Exercise Physiology*, vol. 54, no. 5, pp. 1314–1323, 1983.

[4] A. Crisafulli, F. Tocco, G. Pittau et al., "Detection of lactate threshold by including haemodynamic and oxygen extraction data," *Physiological Measurement*, vol. 27, no. 1, pp. 85–97, 2006.

[5] M. B. Higginbotham, K. G. Morris, R. S. Williams, P. A. McHale, R. E. Coleman, and F. R. Cobb, "Regulation of stroke volume during submaximal and maximal upright exercise in normal man," *Circulation Research*, vol. 58, no. 2, pp. 281–291, 1986.

[6] A. L. Green and D. J. Paterson, "Identification of neurocircuitry controlling cardiovascular function in humans using functional neurosurgery: implications for exercise control," *Experimental Physiology*, vol. 93, no. 9, pp. 1022–1028, 2008.

[7] P. G. Guyenet, "The sympathetic control of blood pressure," *Nature Reviews Neuroscience*, vol. 7, no. 5, pp. 335–346, 2006.

[8] D. I. McCloskey and J. H. Mitchell, "Reflex cardiovascular and respiratory responses originating in exercising muscle," *The Journal of Physiology*, vol. 224, no. 1, pp. 173–186, 1972.

[9] S. Strange, N. H. Secher, J. A. Pawelczyk et al., "Neural control of cardiovascular responses and of ventilation during dynamic exercise in man," *Journal of Physiology*, vol. 470, pp. 693–704, 1993.

[10] L. B. Rowell and D. S. O'Leary, "Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes," *Journal of Applied Physiology*, vol. 69, no. 2, pp. 407–418, 1990.

[11] J. M. Thornton, T. Aziz, D. Schlugman, and D. J. Paterson, "Electrical stimulation of the midbrain increases heart rate and arterial blood pressure in awake humans," *Journal of Physiology*, vol. 539, no. 2, pp. 615–621, 2002.

[12] D. S. O'Leary, "Autonomic mechanisms of muscle metaboreflex control of heart rate," *Journal of Applied Physiology*, vol. 74, no. 4, pp. 1748–1754, 1993.

[13] M. Piepoli, A. L. Clark, and A. J. S. Coats, "Muscle metaboreceptors in hemodynamic, autonomic, and ventilatory responses to exercise in men," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 269, no. 4, pp. H1428–H1436, 1995.

[14] F. Iellamo, P. Pizzinelli, M. Massaro, G. Raimondi, G. Peruzzi, and J. M. Legramante, "Muscle metaboreflex contribution to sinus node regulation during static exercise: insights from spectral analysis of heart rate variability," *Circulation*, vol. 100, no. 1, pp. 27–32, 1999.

[15] A. Crisafulli, A. C. Scott, R. Wensel et al., "Muscle metaboreflex-induced increases in stroke volume," *Medicine and Science in Sports and Exercise*, vol. 35, no. 2, pp. 221–228, 2003.

[16] A. C. L. Nobrega, D. O'Leary, B. M. Silva, E. Marongiu, M. F. Piepoli, and A. Crisafulli, "Neural regulation of cardiovascular response to exercise: role of central command and peripheral afferents," *BioMed Research International*, vol. 2014, Article ID 478965, 20 pages, 2014.

[17] P. J. Fadel, S. Ogoh, D. E. Watenpaugh et al., "Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 280, no. 3, pp. H1383–H1390, 2001.

[18] D. D. Sheriff, "Baroreflex resetting during exercise: mechanisms and meaning," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 290, no. 4, pp. H1406–H1407, 2006.

[19] P. B. Raven, P. J. Fadel, and S. Ogoh, "Arterial baroreflex resetting during exercise: a current perspective," *Experimental Physiology*, vol. 91, no. 1, pp. 37–49, 2006.

[20] M. Alam and F. H. Smirk, "Observations in man upon a blood pressure raising reflex arising from the voluntary muscles," *The Journal of Physiology*, vol. 89, no. 4, pp. 372–383, 1937.

[21] M. Alam and F. H. Smirk, "Observations in man on a pulse-accelerating reflex from the voluntary muscles of the legs," *The Journal of Physiology*, vol. 92, no. 2, pp. 167–177, 1938.

[22] J. H. Coote, S. M. Hilton, and J. F. Perez-Gonzalez, "The reflex nature of the pressor response to muscular exercise," *The Journal of Physiology*, vol. 215, no. 3, pp. 789–804, 1971.

[23] M. P. Kaufman, J. C. Longhurst, K. J. Rybicki, J. H. Wallach, and J. H. Mitchell, "Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats," *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, vol. 55, no. 1 I, pp. 105–112, 1983.

[24] C. M. Adreani, J. M. Hill, and M. P. Kaufman, "Responses of group III and IV muscle afferents to dynamic exercise," *Journal of Applied Physiology*, vol. 82, no. 6, pp. 1811–1817, 1997.

[25] J. Cui, V. Mascarenhas, R. Moradkhan, C. Blaha, and L. I. Sinoway, "Effects of muscle metabolites on responses of muscle sympathetic nerve activity to mechanoreceptor(s) stimulation in healthy humans," *The American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 294, no. 2, pp. R458–R466, 2008.

[26] M. P. Kaufman and K. J. Rybicki, "Discharge properties of group III and IV muscle afferents: their responses to mechanical and metabolic stimuli," *Circulation Research*, vol. 61, no. 4, pp. 160–165, 1987.

[27] S. A. Smith, J. H. Mitchell, and M. G. Garry, "The mammalian exercise pressor reflex in health and disease," *Experimental Physiology*, vol. 91, no. 1, pp. 89–102, 2006.

[28] M. D. Muller, R. C. Drew, J. Cui, C. A. Blaha, J. L. Mast, and L. I. Sinoway, "Effect of oxidative stress on sympathetic and renal vascular responses to ischemic exercise," *Physiological Reports*, vol. 1, no. 3, Article ID e00047, 2013.

[29] T. Nishiyasu, H. Ueno, M. Nishiyasu et al., "Relationship between mean arterial pressure and muscle cell pH during forearm ischaemia after sustained handgrip," *Acta Physiologica Scandinavica*, vol. 150, no. 5, pp. 143–148, 1994.

[30] R. G. Victor, L. A. Bertocci, S. L. Pryor, and R. L. Nunnally, "Sympathetic nerve discharge is coupled to muscle cell pH during exercise in humans," *Journal of Clinical Investigation*, vol. 82, no. 4, pp. 1301–1305, 1988.

[31] J. A. Cornett, M. D. Herr, K. S. Gray, M. B. Smith, Q. X. Yang, and L. I. Sinoway, "Ischemic exercise and the muscle metaboreflex," *Journal of Applied Physiology*, vol. 89, no. 4, pp. 1432–1436, 2000.

[32] M. Amann, G. M. Blain, L. T. Proctor, J. J. Sebranek, D. F. Pegelow, and J. A. Dempsey, "Group III and IV muscle afferents contribute to ventilatory and cardiovascular response to rhythmic exercise in humans," *Journal of Applied Physiology*, vol. 109, no. 4, pp. 966–976, 2010.

[33] M. Amann, G. M. Blain, L. T. Proctor, J. J. Sebranek, D. F. Pegelow, and J. A. Dempsey, "Implications of group III and IV muscle afferents for high-intensity endurance exercise performance in humans," *Journal of Physiology*, vol. 589, no. 21, pp. 5299–5309, 2011.

[34] A. Crisafulli, E. Salis, G. Pittau et al., "Modulation of cardiac contractility by muscle metaboreflex following efforts of different intensities in humans," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 291, no. 6, pp. H3035–H3042, 2006.

[35] A. Crisafulli, R. Milia, A. Lobina et al., "Haemodynamic effect of metaboreflex activation in men after running above and below the velocity of the anaerobic threshold," *Experimental Physiology*, vol. 93, no. 4, pp. 447–457, 2008.

[36] A. Crisafulli, R. Milia, S. Vitelli et al., "Hemodynamic responses to metaboreflex activation: insights from spinal cord-injured humans," *European Journal of Applied Physiology*, vol. 106, no. 4, pp. 525–533, 2009.

[37] S. Roberto, E. Marongiu, M. Pinna et al., "Altered hemodynamics during muscle metaboreflex in young, type 1 diabetes patients," *Journal of Applied Physiology*, vol. 113, no. 8, pp. 1323–1331, 2012.

[38] E. Marongiu, M. Piepoli, R. Milia et al., "Effects of acute vasodilation on the hemodynamic response to muscle metaboreflex," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 305, no. 9, pp. H1387–H1396, 2013.

[39] J. P. Fisher, A. M. Adlan, A. Shantsila, J. F. Secher, H. Sørensen, and N. H. Secher, "Muscle metaboreflex and autonomic regulation of heart rate in humans," *The Journal of Physiology*, vol. 591, no. 15, pp. 3777–3788, 2013.

[40] A. Crisafulli, F. Piras, M. Filippi et al., "Role of heart rate and stroke volume during muscle metaboreflex-induced cardiac output increase: differences between activation during and after exercise," *Journal of Physiological Sciences*, vol. 61, no. 5, pp. 385–394, 2011.

[41] B. G. Bastos, J. W. Williamson, T. Harrelson, and A. C. L. Da Nóbrega, "Left ventricular volumes and hemodynamic responses to postexercise ischemia in healthy humans,"

Medicine and Science in Sports and Exercise, vol. 32, no. 6, pp. 1114–1118, 2000.

[42] M. J. Ichinose, J. A. Sala-Mercado, M. Coutsos et al., "Modulation of cardiac output alters the mechanisms of the muscle metaboreflex pressor response," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 298, no. 1, pp. H245–H250, 2010.

[43] R. Milia, S. Roberto, G. Mulliri et al., "Effect of aging on hemodynamic response to metaboreflex activation," *European Journal of Applied Physiology*, vol. 115, no. 8, pp. 1693–1703, 2015.

[44] D. S. O'Leary and R. A. Augustyniak, "Muscle metaboreflex increases ventricular performance in conscious dogs," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 275, no. 1, pp. H220–H224, 1998.

[45] J. A. Sala-Mercado, R. L. Hammond, J.-K. Kim, N. F. Rossi, L. W. Stephenson, and D. S. O'Leary, "Muscle metaboreflex control of ventricular contractility during dynamic exercise," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 290, no. 2, pp. H751–H757, 2006.

[46] M. D. Spranger, J. A. Sala-Mercado, M. Coutsos et al., "Role of cardiac output versus peripheral vasoconstriction in mediating muscle metaboreflex pressor responses: dynamic exercise versus postexercise muscle ischemia," *The American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 304, no. 8, pp. R657–R663, 2013.

[47] A. Crisafulli, E. Salis, F. Tocco et al., "Impaired central hemodynamic response and exaggerated vasoconstriction during muscle metaboreflex activation in heart failure patients," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 292, no. 6, pp. H2988–H2996, 2007.

[48] M. F. Piepoli, K. Dimopoulos, A. Concu, and A. Crisafulli, "Cardiovascular and ventilatory control during exercise in chronic heart failure: role of muscle reflexes," *International Journal of Cardiology*, vol. 130, no. 1, pp. 3–10, 2008.

[49] D. D. Sheriff, R. A. Augustyniak, and D. S. O'Leary, "Muscle chemoreflex-induced increases in right atrial pressure," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 275, no. 3, pp. H767–H775, 1998.

[50] R. Milia, S. Roberto, E. Marongiu et al., "Improvement in hemodynamic responses to metaboreflex activation after one year of training in spinal cord injured humans," *BioMed Research International*, vol. 2014, Article ID 893468, 9 pages, 2014.

[51] J. K. Shoemaker, L. Mattar, P. Kerbeci, S. Trotter, P. Arbeille, and R. L. Hughson, "WISE 2005: stroke volume changes contribute to the pressor response during ischemic handgrip exercise in women," *Journal of Applied Physiology*, vol. 103, no. 1, pp. 228–233, 2007.

[52] A. P. Hollander and L. N. Bouman, "Cardiac acceleration in man elicited by a muscle heart reflex," *Journal of Applied Physiology*, vol. 38, no. 2, pp. 272–278, 1975.

[53] J. P. Fisher and M. J. White, "Muscle afferent contributions to the cardiovascular response to isometric exercise," *Experimental Physiology*, vol. 89, no. 6, pp. 639–646, 2004.

[54] A. Krogh and J. Lindhard, "The regulation of respiration and circulation during the initial stages of muscular work," *The Journal of Physiology*, vol. 47, no. 1-2, pp. 112–136, 1913.

[55] G. M. Goodwin, D. I. McCloskey, and J. H. Mitchell, "Cardiovascular and respiratory responses to changes in central command during isometric exercise at constant muscle tension," *The Journal of Physiology*, vol. 226, no. 1, pp. 173–190, 1972.

[56] A. C. L. Nobrega and C. G. S. Araujo, "Heart rate transient at the onset of active and passive dynamic exercise," *Medicine and Science in Sports and Exercise*, vol. 25, no. 1, pp. 37–41, 1993.

[57] J. W. Williamson, A. C. L. Nobrega, P. K. Winchester, S. Zim, and J. H. Mitchell, "Instantaneous heart rate increase with dynamic exercise: central command and muscle-heart reflex contributions," *Journal of Applied Physiology*, vol. 78, no. 4, pp. 1273–1279, 1995.

[58] J. W. Williamson, "Autonomic responses to exercise: where is central command?" *Autonomic Neuroscience: Basic and Clinical*, vol. 188, pp. 3–4, 2015.

[59] A. L. Green, S. Wang, S. Purvis et al., "Identifying cardiorespiratory neurocircuitry involved in central command during exercise in humans," *Journal of Physiology*, vol. 578, no. 2, pp. 605–612, 2007.

[60] J. K. Shoemaker, K. N. Norton, J. Baker, and T. Luchyshyn, "Forebrain organization for autonomic cardiovascular control," *Autonomic Neuroscience: Basic and Clinical*, vol. 188, pp. 5–9, 2015.

[61] J. W. Williamson, R. McColl, D. Mathews, M. Ginsburg, and J. H. Mitchell, "Activation of the insular cortex is affected by the intensity of exercise," *Journal of Applied Physiology*, vol. 87, no. 3, pp. 1213–1219, 1999.

[62] J. W. Williamson, R. McColl, and D. Mathews, "Evidence for central command activation of the human insular cortex during exercise," *Journal of Applied Physiology*, vol. 94, no. 5, pp. 1726–1734, 2003.

[63] S. D. Basnayake, J. A. Hyam, E. A. Pereira et al., "Identifying cardiovascular neurocircuitry involved in the exercise pressor reflex in humans using functional neurosurgery," *Journal of Applied Physiology*, vol. 110, no. 4, pp. 881–891, 2011.

[64] D. J. Paterson, "Defining the neurocircuitry of exercise hyperpnoea," *Journal of Physiology*, vol. 592, no. 3, pp. 433–444, 2014.

[65] K. Sagawa and A. Eisner, "Static pressure flow relation in the total systemic vascular bed of the dog and its modification by the baroreceptor reflex," *Circulation Research*, vol. 36, no. 3, pp. 406–413, 1975.

[66] P. J. Fadel and P. B. Raven, "Human investigations into the arterial and cardiopulmonary baroreflexes during exercise," *Experimental Physiology*, vol. 97, no. 1, pp. 39–50, 2012.

[67] B. S. Bevegård and J. T. Shepherd, "Circulatory effects of stimulating the carotid arterial stretch receptors in man at rest and during exercise," *The Journal of Clinical Investigation*, vol. 45, no. 1, pp. 132–142, 1966.

[68] T. G. Pickering, B. Gribbin, E. S. Petersen, D. J. C. Cunningham, and P. Sleight, "Comparison of the effects of exercise and posture on the baroreflex in man," *Cardiovascular Research*, vol. 5, no. 4, pp. 582–586, 1971.

[69] D. J. Cunningham, E. S. Petersen, R. Peto, T. G. Pickering, and P. Sleight, "Comparison of the effect of different types of exercise on the baroreflex regulation of heart rate," *Acta Physiologica Scandinavica*, vol. 86, no. 4, pp. 444–455, 1972.

[70] T. G. Pickering, B. Gribbin, E. S. Petersen, D. J. Cunningham, and P. Sleight, "Effects of autonomic blockade on the baroreflex in man at rest and during exercise," *Circulation Research*, vol. 30, no. 2, pp. 177–185, 1972.

[71] M. J. Joyner, "Baroreceptor function during exercise: resetting the record," *Experimental Physiology*, vol. 91, no. 1, pp. 27–36, 2006.

[72] P. B. Raven, J. T. Potts, and X. Shi, "Baroreflex regulation of blood pressure during dynamic exercise," *Exercise and Sport Sciences Reviews*, vol. 25, pp. 365–389, 1997.

[73] F. Iellamo, J. M. Legramante, G. Raimondi, and G. Peruzzi, "Baroreflex control of sinus node during dynamic exercise in humans: effects of central command and muscle reflexes," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 41, no. 3, pp. H1157–H1164, 1997.

[74] F. Iellamo, "Baroreflex control of heart rate during exercise: a topic of perennial conflict," *Journal of Applied Physiology*, vol. 90, no. 3, pp. 1184–1185, 2001.

[75] J. T. Potts, X. R. Shi, and P. B. Raven, "Carotid baroreflex responsiveness during dynamic exercise in humans," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 265, no. 6, pp. H1928–H1938, 1993.

[76] S. Ogoh, J. P. Fisher, E. A. Dawson, M. J. White, N. H. Secher, and P. B. Raven, "Autonomic nervous system influence on arterial baroreflex control of heart rate during exercise in humans," *Journal of Physiology*, vol. 566, no. 2, pp. 599–611, 2005.

[77] S. Ogoh, P. J. Fadel, P. Nissen et al., "Baroreflex-mediated changes in cardiac output and vascular conductance in response to alterations in carotid sinus pressure during exercise in humans," *The Journal of Physiology*, vol. 550, no. 1, pp. 317–324, 2003.

[78] P. J. Fadel, S. Ogoh, D. M. Keller, and P. B. Raven, "Recent insights into carotid baroreflex function in humans using the variable pressure neck chamber," *Experimental Physiology*, vol. 88, no. 6, pp. 671–680, 2003.

[79] Y. Papelier, P. Escourrou, J. P. Gauthier, and L. B. Rowell, "Carotid baroreflex control of blood pressure and heart rate in men during dynamic exercise," *Journal of Applied Physiology*, vol. 77, no. 2, pp. 502–506, 1994.

[80] K. H. Norton, R. Boushel, S. Strange, B. Saltin, and P. B. Raven, "Resetting of the carotid arterial baroreflex during dynamic exercise in humans," *Journal of Applied Physiology*, vol. 87, no. 1, pp. 332–338, 1999.

[81] S. C. Walgenbach and D. E. Donald, "Inhibition by carotid baroreflex of exercise-induced increases in arterial pressure," *Circulation Research*, vol. 52, no. 3, pp. 253–262, 1983.

[82] A. A. J. Smit, H. J. L. M. Timmers, W. Wieling et al., "Long-term effects of carotid sinus denervation on arterial blood pressure in humans," *Circulation*, vol. 105, no. 11, pp. 1329–1335, 2002.

[83] H. J. L. M. Timmers, W. Wieling, J. M. Karemaker, and J. W. M. Lenders, "Cardiovascular responses to stress after carotid baroreceptor denervation in humans," *Annals of the New York Academy of Sciences*, vol. 1018, pp. 515–519, 2004.

[84] U. Scherrer, S. L. Pryor, L. A. Bertocci, and R. G. Victor, "Arterial baroreflex buffering of sympathetic activation during exercise-induced elevations in arterial pressure," *Journal of Clinical Investigation*, vol. 86, no. 6, pp. 1855–1861, 1990.

[85] J. Hansen, G. D. Thomas, T. N. Jacobsen, and R. G. Victor, "Muscle metaboreflex triggers parallel sympathetic activation in exercising and resting human skeletal muscle," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 266, no. 6, pp. H2508–H2514, 1994.

[86] G. D. Thomas, J. Hansen, and R. G. Victor, "Inhibition of alpha 2-adrenergic vasoconstriction during contraction of glycolytic, not oxidative, rat hindlimb muscle," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 266, no. 3, pp. H920–H929, 1994.

[87] J. Hansen, G. D. Thomas, S. A. Harris, W. J. Parsons, and R. G. Victor, "Differential sympathetic neural control of oxygenation in resting and exercising human skeletal muscle," *The Journal of Clinical Investigation*, vol. 98, no. 2, pp. 584–596, 1996.

[88] G. D. Thomas, M. Sander, K. S. Lau, P. L. Huang, J. T. Stull, and R. G. Victor, "Impaired metabolic modulation of α-adrenergic vasoconstriction in dystrophin-deficient skeletal muscle," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 25, pp. 15090–15095, 1998.

[89] J. Hansen, M. Sander, and G. D. Thomas, "Metabolic modulation of sympathetic vasoconstriction in exercising skeletal muscle," *Acta Physiologica Scandinavica*, vol. 168, no. 4, pp. 489–503, 2000.

[90] J. B. Buckwalter and P. S. Clifford, "The paradox of sympathetic vasoconstriction in exercising skeletal muscle," *Exercise and Sport Sciences Reviews*, vol. 29, no. 4, pp. 159–163, 2001.

[91] J. B. Buckwalter, J. S. Naik, Z. Valic, and P. S. Clifford, "Exercise attenuates α-adrenergic-receptor responsiveness in skeletal muscle vasculature," *Journal of Applied Physiology*, vol. 90, no. 1, pp. 172–178, 2001.

[92] S. B. Ruble, Z. Valic, J. B. Buckwalter, M. E. Tschakovsky, and P. S. Clifford, "Attenuated vascular responsiveness to noradrenaline release during dynamic exercise in dogs," *The Journal of Physiology*, vol. 541, no. 2, pp. 637–644, 2002.

[93] M. E. Tschakovsky, K. Sujirattanawimol, S. B. Ruble, Z. Valic, and M. J. Joyner, "Is sympathetic neural vasoconstriction blunted in the vascular bed of exercising human muscle?" *The Journal of Physiology*, vol. 541, no. 2, pp. 623–635, 2002.

[94] M. Sander, B. Chavoshan, S. A. Harris et al., "Functional muscle ischemia in neuronal nitric oxide synthase-deficient skeletal muscle of children with Duchenne muscular dystrophy," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 25, pp. 13818–13823, 2000.

[95] B. Chavoshan, M. Sander, T. E. Sybert, J. Hansen, R. G. Victor, and G. D. Thomas, "Nitric oxide-dependent modulation of sympathetic neural control of oxygenation in exercising human skeletal muscle," *The Journal of Physiology*, vol. 540, no. 1, pp. 377–386, 2002.

[96] J. M. Quayle and N. B. Standen, "KATP channels in vascular smooth muscle," *Cardiovascular Research*, vol. 28, no. 6, pp. 797–804, 1994.

[97] M. T. Nelson and J. M. Quayle, "Physiological roles and properties of potassium channels in arterial smooth muscle," *The American Journal of Physiology—Cell Physiology*, vol. 268, no. 4, pp. C799–C822, 1995.

[98] D. M. Keller, S. Ogoh, S. Greene, A. Olivencia-Yurvati, and P. B. Raven, "Inhibition of KATP channel activity augments baroreflex-mediated vasoconstriction in exercising human skeletal muscle," *The Journal of Physiology*, vol. 561, no. 1, pp. 273–282, 2004.

[99] J. P. Cooke, J. T. Shepherd, and P. M. Vanhoutte, "The effect of warming on adrenergic neurotransmission in canine cutaneous vein," *Circulation Research*, vol. 54, no. 5, pp. 547–553, 1984.

[100] J. Hansen, M. Sander, C. F. Hald, R. G. Victor, and G. D. Thomas, "Metabolic modulation of sympathetic vasoconstriction in human skeletal muscle: role of tissue hypoxia," *The Journal of Physiology*, vol. 527, no. 2, pp. 387–396, 2000.

[101] K. M. McGillivray-Anderson and J. E. Faber, "Effect of acidosis on contraction of microvascular smooth muscle by α1- and α2-adrenoceptors. Implications for neural and metabolic regulation," *Circulation Research*, vol. 66, no. 6, pp. 1643–1657, 1990.

[102] D. M. Keller, P. J. Fadel, S. Ogoh et al., "Carotid baroreflex control of leg vasculature in exercising and non-exercising skeletal muscle in humans," *Journal of Physiology*, vol. 561, no. 1, pp. 283–293, 2004.

[103] S. Ogoh, W. L. Wasmund, D. M. Keller et al., "Role of central command in carotid baroreflex resetting in humans during static exercise," *Journal of Physiology*, vol. 543, no. 1, pp. 349–364, 2002.

[104] S. A. McIlveen, S. G. Hayes, and M. P. Kaufman, "Both central command and exercise pressor reflex reset carotid sinus baroreflex," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 280, no. 4, pp. H1454–H1463, 2001.

[105] R. G. Querry, S. A. Smith, M. Strømstad, K. Ide, P. B. Raven, and N. H. Secher, "Neural blockade during exercise augments central command's contribution to carotid baroreflex resetting," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 280, no. 4, pp. H1635–H1644, 2001.

[106] K. M. Gallagher, P. J. Fadel, M. Strømstad et al., "Effects of partial neuromuscular blockade on carotid baroreflex function during exercise in humans," *The Journal of Physiology*, vol. 533, no. 3, pp. 861–870, 2001.

[107] Y. Papelier, P. Escourrou, F. Helloco, and L. B. Rowell, "Muscle chemoreflex alters carotid sinus baroreflex response in humans," *Journal of Applied Physiology*, vol. 82, no. 2, pp. 577–583, 1997.

[108] O. Eiken, V. A. Convertino, D. F. Doerr, G. A. Dudley, G. Morariu, and I. B. Mekjavic, "Characteristics of the carotid baroreflex in man during normal and flow-restricted exercise," *Acta Physiologica Scandinavica*, vol. 144, no. 3, pp. 325–331, 1992.

[109] X. Shi, J. T. Potts, B. H. Foresman, and P. B. Raven, "Carotid baroreflex responsiveness to lower body positive pressure-induced increases in central venous pressure," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 265, no. 3, pp. H918–H922, 1993.

[110] K. M. Gallagher, P. J. Fadel, M. Strømstad et al., "Effects of exercise pressor reflex activation on carotid baroreflex function during exercise in humans," *The Journal of Physiology*, vol. 533, no. 3, pp. 871–880, 2001.

[111] K. M. Gallagher, P. J. Fadel, S. A. Smith et al., "The interaction of central command and the exercise pressor reflex in mediating baroreflex resetting during exercise in humans," *Experimental Physiology*, vol. 91, no. 1, pp. 79–87, 2006.

[112] T. Nishiyasu, N. Tan, K. Morimoto, M. Nishiyasu, Y. Yamaguchi, and N. Murakami, "Enhancement of parasympathetic cardiac activity during activation of muscle metaboreflex in humans," *Journal of Applied Physiology*, vol. 77, no. 6, pp. 2778–2783, 1994.

[113] G. Mack, H. Nose, and E. R. Nadel, "Role of cardiopulmonary baroreflexes during dynamic exercise," *Journal of Applied Physiology*, vol. 65, no. 4, pp. 1827–1832, 1988.

[114] R. L. H. Sprangers, K. H. Wesseling, A. L. T. Imholz, B. P. M. Impholz, and W. Wieling, "Initial blood pressure fall on stand up and exercise explained by changes in total peripheral resistance," *Journal of Applied Physiology*, vol. 70, no. 2, pp. 523–530, 1991.

[115] H. Koike, A. L. Mark, D. D. Heistad, and P. G. Schmid, "Influence of cardiopulmonary vagal afferent activity on carotid chemoreceptor and baroreceptor reflexes in the dog," *Circulation Research*, vol. 37, no. 4, pp. 422–429, 1975.

[116] S. Bevegard, J. Castenfors, and L. E. Lindblad, "Effect of carotid sinus stimulation on cardiac output and peripheral vascular resistance during changes in blood volume distribution in man," *Acta Physiologica Scandinavica*, vol. 101, no. 1, pp. 50–57, 1977.

[117] S. Bevegard, J. Castenfors, L. E. Lindblad, and J. Tranesjo, "Blood pressure and heart rate regulating capacity of the carotid sinus during changes in blood volume distribution in man," *Acta Physiologica Scandinavica*, vol. 99, no. 3, pp. 300–312, 1977.

[118] J. A. Pawelczyk and P. B. Raven, "Reductions in central venous pressure improve carotid baroreflex responses in conscious men," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 257, no. 5, pp. H1389–H1395, 1989.

[119] J. T. Potts, X. Shi, and P. B. Raven, "Cardiopulmonary baroreceptors modulate carotid baroreflex control of heart rate during dynamic exercise in humans," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 268, no. 4, pp. H1567–H1576, 1995.

[120] S. Volianitis, C. C. Yoshiga, T. Vogelsang, and N. H. Secher, "Arterial blood pressure and carotid baroreflex function during arm and combined arm and leg exercise in humans," *Acta Physiologica Scandinavica*, vol. 181, no. 3, pp. 289–295, 2004.

[121] S. Ogoh, R. M. Brothers, Q. Barnes et al., "Effects of changes in central blood volume on carotid-vasomotor baroreflex sensitivity at rest and during exercise," *Journal of Applied Physiology*, vol. 101, no. 1, pp. 68–75, 2006.

[122] S. Ogoh, J. P. Fisher, P. J. Fadel, and P. B. Raven, "Increases in central blood volume modulate carotid baroreflex resetting during dynamic exercise in humans," *Journal of Physiology*, vol. 581, no. 1, pp. 405–418, 2007.

[123] S. Ogoh, R. M. Brothers, Q. Barnes et al., "Cardiopulmonary baroreflex is reset during dynamic exercise," *Journal of Applied Physiology*, vol. 100, no. 1, pp. 51–59, 2006.

[124] M. Amann, L. T. Proctor, J. J. Sebranek, M. W. Eldridge, D. F. Pegelow, and J. A. Dempsey, "Somatosensory feedback from the limbs exerts inhibitory influences on central neural drive during whole body endurance exercise," *Journal of Applied Physiology*, vol. 105, no. 6, pp. 1714–1724, 2008.

[125] M. Amann, S. Runnels, D. E. Morgan et al., "On the contribution of group III and IV muscle afferents to the circulatory response to rhythmic exercise in humans," *Journal of Physiology*, vol. 589, no. 15, pp. 3855–3866, 2011.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 591708, 8 pages
http://dx.doi.org/10.1155/2015/591708

Review Article

Effects of Exercise Training on Autonomic Function in Chronic Heart Failure: Systematic Review

Chung-Yin Hsu,[1] Ping-Lun Hsieh,[2,3] Shu-Fang Hsiao,[4] and Meng-Yueh Chien[3,5]

[1]*Department of Physical Therapy and Rehabilitation, Zhongxing Branch of Taipei City Hospital, Taipei 10341, Taiwan*
[2]*Department of Rehabilitation, Keelung Hospital, Ministry of Health and Welfare, Keelung 20147, Taiwan*
[3]*School and Graduate Institute of Physical Therapy, College of Medicine, National Taiwan University, Taipei 10051, Taiwan*
[4]*Department of Physical Therapy and Rehabilitation, National Taiwan University Hospital, Taipei 10002, Taiwan*
[5]*Physical Therapy Center of National Taiwan University Hospital, Taipei 10002, Taiwan*

Correspondence should be addressed to Meng-Yueh Chien; mychien@ntu.edu.tw

Received 29 May 2015; Revised 10 September 2015; Accepted 13 September 2015

Academic Editor: Andrew J. Coats

Objectives. Cardiac autonomic imbalance accompanies the progression of chronic heart failure (CHF). It is unclear whether exercise training could modulate autonomic control in CHF. This study aimed to review systematically the effects of exercise training on heart rate recovery (HRR) and heart rate variability (HRV) in patients with CHF. *Methods*. Literatures were systematically searched in electronic databases and relevant references. Only published randomized controlled trials (RCTs) focusing on exercise training for CHF were eligible for inclusion. Outcome measurements included HRR and HRV parameters. *Results*. Eight RCTs were eligible for inclusion and provided data on 280 participants (186 men). The participants were 52–70 years of age with New York Heart Association functional class II-III of CHF. Each study examined either aerobic or resistance exercise. Two trials addressed outcome of HRR and six HRV among these studies. Two RCTs showed that moderate aerobic exercise could improve HRR at 2 minutes after exercise training in CHF. Five of six RCTs demonstrated positive effects of exercise training on HRV which revealed the increments in high frequency (HF) and decrements in LF (low frequency)/HF ratio after training. *Conclusion*. Participation in an exercise training program has positive effects on cardiac autonomic balance in patients with CHF.

1. Introduction

Chronic heart failure (CHF), the common final stage of all heart diseases with negative impact on prognosis, is increasingly prevalent worldwide and is associated with significant morbidity and mortality [1, 2]. Exercise intolerance is one of the major symptoms of CHF which can be contributed to several factors, including reduced cardiac output, cardiac cachexia, and neurohormonal axis changes [3, 4]. Autonomic imbalance includes increase in sympathetic tone, decrease in parasympathetic activity, and depressed heart rate variability (HRV) [5], which is a common clinical predictor of poor survival in CHF [6, 7]. Autonomic modulation is consequently an important issue of modern heart failure management.

The heart rate response to exercise and recovery from exercise depends on the dynamic interaction between the sympathetic and parasympathetic nervous systems [8]. Heart rate recovery (HRR) after exercise termination is mediated by a combination of sympathetic withdrawal and parasympathetic reactivation, primarily by vagal reactivation [9]. Slow HRR has been reported to be important in predicting mortality in healthy individuals [10] and people with heart failure [11]. HRR at 1 minute after exercise termination (HRR_1) was thus used as a simple measure indicative of decreased autonomic nervous system activity [12]. HRV is another noninvasive and easy-to-obtain measurement of cardiac autonomic system function. HRV is defined as beat-to-beat variations in heart rate of individuals in sinus rhythm [13]. Reduced HRV generally indicates either failure or attenuation in the autonomic regulation of the sinoatrial node [13]. Although HRV and HRR do not directly measure autonomic nervous activity, both are considered significant prognostic indicators of mortality in CHF by evidence [14–16]. A variety of drugs as well as numerous invasive procedures have been

reported to effectively modify HRV. However, evidence of its adverse events and sustained efficacy is lacking. In view of large number of other drugs that patients with CHF frequently take in conjunction with cardiac medication, an evidence-based nondrug approach is of interest.

Current evidence has recommended exercise training as a key component in the guidelines for secondary prevention of CHF [17]. Research in exercise training confirmed significant improvements of clinically relevant outcome parameters such as exercise capacity, quality of life, and CHF related hospitalization [18–20]. However, these studies were not designed to exclusively address outcome parameters such as HRV and HRR in patients with CHF. Aerobic exercise and physical training have been shown to improve HRV in various populations, such as athletes and sedentary individuals [21], and patients with cardiovascular diseases [22]. Despite the fact that exercise training is recommended as an adjunct to clinical therapy in patients with CHF [17], limited published data exist to evaluate HRV and HRR after exercise training in CHF. Because of easy access and a low cost, exercise training may be an alternative and favorable approach to existing therapies for prevention and treatment of autonomic imbalance among CHF populations. Therefore, our objective of this systematic review was to investigate the effects of exercise training on HRR and HRV in patients with CHF.

2. Methods

2.1. Identification and Selection of Trials. Five electronic databases (PubMed, the Cumulative Index to Nursing and Allied Health Literature [CINAHL], EMBASE, the Cochrane Library, and Chinese Electronic Periodical Service [Airiti Library]) from the earliest available date to March 2015 using various combinations of keywords for heart failure (*congestive heart failure, chronic heart failure*), for exercise (*exercise training, physical training*), and for autonomic (*autonomic function, heart rate recovery, heart rate variability*) were processed. We limited the search results to full-text articles in English or Chinese. We then checked the reference lists of the original and review articles that the initial search had yielded in order to identify additional full-text articles.

The inclusion criteria are presented as follows.

Design

(i) Randomized trial.

Participants

(i) Chronic heart failure.

(ii) Ejection fraction < 40%.

Intervention

(i) Exercise training program (aerobic or resistance exercise).

Outcome Measures

(i) Heart rate recovery.

(ii) Heart rate variability.

Control

(i) No training or usual care.

Randomized controlled trials (RCTs) eligible for subsequent criteria were included in this systematic review. Interventions were based exclusively on exercise training, aerobic or resistance training modules alone, or the combination of both. Trials were excluded if the group allocations are not pure control group of CHF patients versus an exercise group and if the other forms of physical therapy were applied.

Two reviewers (Hsieh and Hsu) independently reviewed the articles to determine whether the articles met the predetermined eligibility criteria. The results were rechecked by the senior authors (Hsiao and Chien), and all reviewers resolved any disagreement and ambiguous or equivocal information through discussion and writing letter of confirmation to the authors to reach a consensus in every relevant detail. In cases of multiple publications arising from a single trial, only the report that contained the most detailed, updated, and quantified information regarding both intervention and outcomes was included.

2.2. Assessment of Characteristics of Trials

Quality. The methodological quality of the selected trials was independently assessed by two reviewers (Hsieh and Hsu) using the Physiotherapy Evidence Database (PEDro) scale. Any disagreement with regard to methodological quality was resolved through discussion and consensus.

Participants. Demographic data such as age, gender, New York Heart Association (NYHA) functional class, and ejection fraction (EF) were recorded to characterize the trials and to determine the homogeneity of participants between groups and between trials.

Intervention. The target intensity, duration, frequency and the total period of time for exercise training program, and the nature of the control group were recorded.

Outcome Measures. The measured outcomes we considered were HRR at 1 or 2 minutes after exercise termination (HRR_1, HRR_2) and time domain of HRV (RR interval, standard deviation of all RR intervals [SDNN], root mean square of difference in RR intervals [RMSSD]), and percentage difference between adjacent NN intervals (pNN) and frequency domain of HRV (high frequency (HF), low frequency (LF), and LF/HF ratio).

3. Results

3.1. Flow of Studies through the Review. Initially, 231 studies have been identified through the database search of which 16 were considered potentially relevant and respected the previously mentioned inclusion criteria. Out of these, 8 eligible articles were retained for further systematic review after the screening of titles and abstracts [23–30]. Eight articles were subsequently excluded in which 4 trials had their control groups engaged in some forms of exercise [31–34], 2 trials had no control group [35, 36], and 2 trials had control

Table 1: PEDro scores for included trials (n = 8).

Trials	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
Myers et al., 2007 [23]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Yaylali et al., 2015 [24]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Selig et al., 2004 [25]	Y	N	Y	N	N	Y	N	N	Y	Y	5/10
Murad et al., 2012 [26]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Ricca-Mallada et al., 2012 [27]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Kiilavuori et al., 1995 [28]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Yeh et al., 2008 [29]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Cider et al., 1997 [30]	Y	N	N	N	N	Y	Y	Y	Y	N	5/10

N = no; Y = yes.

groups of normal healthy participants that did not meet the inclusion criteria [37, 38] (Figure 1). No additional articles were identified by the scanning of reference lists. Therefore 8 trials were included in the analysis.

3.2. Characteristics of Included Trials. The methodological quality of selected trials assessed by the PEDro scale is shown in Table 1 and a summary of the trials is presented in Table 2.

Quality. Based on the quality of PEDro scale for methodological quality assessment, the RCTs included in this systematic review are of good quality with six trials scoring 7/10 [23, 24, 26–29] and two trials with fair scoring of 5/10 [25, 30]. No trial blinded participants or therapists, while all trials blinded assessors. Most trials had retention rates of 85% or greater and reported between-group differences with point estimates and measures of variability (Table 1).

Participants. The eight included trials involved 280 participants (186 men and 94 women) with sample sizes averaged from 20 to 66 for each study. The majority of the patients were 52–70 years of mean age with at least 6-month diagnosis and treatment of CHF. The subsets of the diagnosis included ischemic, coronary artery, hypertensive, valvular heart disease, and idiopathic dilated cardiomyopathy. Except for 3 trials [23, 27, 29], all the other trials contain patients with NYHA functional class II-III with their EF < 40%. Their comorbidity included hypertension, diabetes, coronary heart disease, prior myocardial infarction, and coronary bypass grafting. The pharmacological therapy included angiotensin-converting enzyme inhibitors, beta-blockers, statins, digoxin, and diuretics.

Interventions. Six trials examined supervised aerobic exercise (walking, cycling ergometer, or Tai Chi) [23, 24, 26–29] and two examined supervised resistance training (multistation hydraulic resistance training or circuit weight training) [25, 30]. The duration of the trials was between 8 and 24 weeks, most trials with 12 weeks. Exercise time for each session of the trials varied from 30 minutes to 1 hour. The frequency

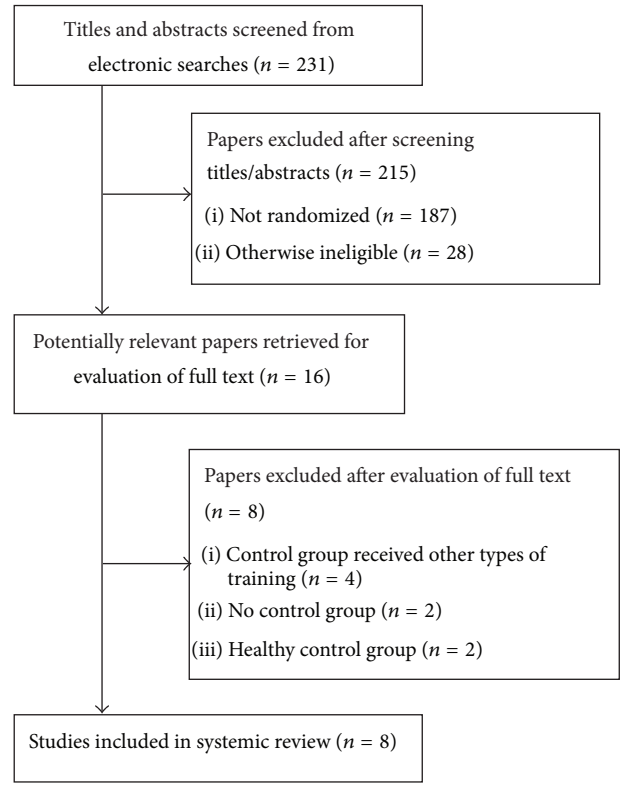


Figure 1: Trial flow diagram of this systemic review.

Table 2: Overview of included randomized control trials ($n = 8$).

Study	Participants	Intervention	Outcome measures	Main results
Myers et al., 2007 [23]	CHF (EF < 40%) Ex: $n = 12$ men, aged 56 ± 5 years Con: $n = 12$ men, aged 55 ± 7 years	Exercise: supervised hospital-based exercise training 1-hour walking and 45 min cycling, 5x/wk for 8 weeks at 60%–80% of heart rate reserve Control: usual care	$HRR_{1–6}$	Exercise group got significant improvements in $HRR_{2–6}$
Yaylali et al., 2015 [24]	CHF (EF < 45%, NYHA II-III) Interval: $n = 13$ men, 4 women, aged 63.7 ± 8.8 years Continuous: $n = 13$ men, aged 59.6 ± 6.8 years Con: $n = 9$ men, 2 women, aged 60.6 ± 9.9 years	Exercise 1 (interval training): 30 minutes of cycle ergometer aerobic exercise 3x/wk for 12 weeks at 50%–75% HRR Exercise 2 (continuous training): exercise protocol similar to interval training group without resting intervals Control: continued with ADL	HRR_1, HRR_2	Interval training group got significant improvements in HRR_2. Unchanged HRR_1 irrespective of any groups
Selig et al., 2004 [25]	CHF (EF < 40%, NYHA II-III) Ex: $n = 15$ men, 4 women, aged 65 ± 13 years Con: $n = 18$ men, 2 women, aged 64 ± 9 years	Exercise: supervised hospital-based 1-hour multistation hydraulic moderate intensity (according to heart rate monitoring) resistance training, 3x/wk for 3 months Control: usual care	Short-run rest ECG HRV: RR interval, SDNN, RMSSD, LF_{nu}, HF_{nu}, and LF/HF	Exercise group got significant decreases in LF, HF, and LF/HF after training
Murad et al., 2012 [26]	CHF (EF < 40%, NYHA II-III) Ex: $n = 11$ men, 20 women, aged 68.0 ± 4.8 years Con: $n = 13$ men, 22 women, aged 70.1 ± 5.6 years	Exercise: supervised hospital-based 1-hour walking and 15–20 minutes of cycling exercise training, 3x/wk for 16 weeks at 40%–50% to 60%–70% heart rate reserve Control: monitored with phone calls every 2 weeks	Short-run rest ECG HRV: SDNN, RMSSD	Exercise group showed significant increases in SDNN and RMSSD compared to controls
Ricca-Mallada et al., 2012 [27]	CHF (EF ≦ 40%, NYHA I-II) Ex: $n = 8$ men, 2 women, aged 59.0 ± 7.9 years Con: $n = 8$ men, 2 women, aged 56.5 ± 8.4 years	Exercise: supervised hospital-based 55-minute circuit bicycle resistance training, 3x/wk for 24 weeks at 50%–80% of HR reserve Control: usual medication	Short-run rest ECG HRV: RR interval, SDNN, LF, HF, and LF/HF	Exercise group got significant increases of mean RR interval, HF, and LF after training
Kilavuori et al., 1995 [28]	CHF (EF < 40%, NYHA II-III) Ex: $n = 8$ men, aged 52 ± 8 years Con: $n = 11$ men, 1 woman, aged 52 ± 10 years	Exercise: supervised hospital-based ergometer cycling for 30 minutes, 3x/wk for 3 months at 50%–60% of VO_{2max} Control: no changing normal ADL	20 h Holter HRV: HF, LF, VLF, LF/HF, and VLF/HF	Exercise group got significant changes in HF, VLF/HF, and LF/HF during the day
Yeh et al., 2008 [29]	CHF (EF ≦ 40%, NYHA I–IV) Ex: $n = 10$ men, 5 women, aged 66 ± 12 years Con: $n = 9$ men, 6 women, aged 61 ± 14 years	Exercise: supervised hospital-based Tai Chi training (1 hour), 2x/wk for 12 weeks Control: usual care	24-hour Holter HRV: SDNN, RMSSD, pNN10–50, LF, HF, and LF/HF	Exercise group showed trends towards increased pNN10–50 values during sleep, but not in the control group

Table 2: Continued.

Study	Participants	Intervention	Outcome measures	Main results
Cider et al., 1997 [30]	CHF (NYHA II-III) Ex: n = 9 men, 12 women, aged 61.8 ± 9.8 years Con: n = 7 men, 12 women, aged 64.7 ± 5.3 years	Exercise: supervised hospital-based 60-minute circuit weight training at 60% 1-RM for 2 sets, 2x/week for 20 weeks Control: usual care	24-hour Holter HRV: time/frequency domain parameters	No significant difference between the two groups in all HRV parameters

ADL: activities of daily living; CHF: chronic heart failure; ECG: electrocardiogram; EF: ejection fraction; HRR: heart rate recovery; HRV: heart rate variability; NYHA: New York Heart Association; pNN10–50: percentage difference between adjacent NN intervals that are greater than 10–50 ms; SDNN: standard deviation of all RR intervals; RMSSD: root mean square of difference in RR intervals; LF: low frequency; HF: high frequency; VLF: very-low frequency; VO_{2max}: maximal oxygen consumption.

of exercise programs was between 2 and 5 times per week, most trials with 3 times per week. The control groups in all the trials received either no treatment or health education. Most aerobic exercise programs examined were of moderate intensity, instructing the participants to reach 50% to 80% of their heart rate reserve or peak oxygen consumption for 20 to 60 minutes (Table 2).

3.3. Effect of Exercise Training on HRR and HRV

3.3.1. Trials with HRR as Outcome Measure for Exercise Training. Two trials investigated the effects of exercise training on HRR [23, 24]. Out of that, one trial evaluated both HRR_1 and HRR_2 [24], and the other utilized HRR_{1-6} as outcome measures [23]. These 2 trials employed 8- and 12-week moderate intensity aerobic exercise training program. The results of both trials showed no significant effect on HRR_1; however, their HRR_2 manifested significant improvement (10.9 and 24 bpm, resp., $P < 0.05$). The results of study by Myers et al. [23] even showed statistically significant improvement in HRR_{2-6} ($P < 0.05$). In summary, it was shown that moderate intensity aerobic exercise training improved HRR in patients with CHF.

3.3.2. Trials with HRV as Outcome Measure for Exercise Training. Six RCTs investigated the effects of exercise training on HRV in which 3 trials employed short-term recordings of HRV [25–27] while 3 others employed 20- to 24-hour Holter electrocardiogram (ECG) recordings of HRV [28–30]. Four out of the 6 trials analyzed HRV parameters in both time and frequency domains. One trial utilized only time domain analysis [26] and one frequency domain [27]. Five trials (4 aerobic exercise program and one resistance exercise program) showed some improvements in time and frequency domain HRV parameters. A significant increase in both SDNN and RMSSD (15.46 and 17.56 ms, resp., $P < 0.05$) after exercise training was reported [26]. In addition, several studies revealed the increments in HF as well as the reduction in LF/HF ratio after exercise training in patients with CHF [25, 27, 28]. Only one trial which consisted of resistance training and HRV parameters obtained by 24-hour Holter did not find any significant change of HRV after exercise training [30]. In an overview of the results, moderate intensity aerobic exercise training was effective to ameliorate HRV in patients with CHF.

3.3.3. Adverse Events. No adverse event relevant to exercise training during these trials occurred or was reported.

4. Discussion

This was the first systematic review providing a comprehensive survey of RCTs which examined the effects of exercise training on autonomic function in patients with CHF. Although the heterogeneity of HRV parameters restricted the direct pooled analysis, the results derived from fair to good quality evidence indicated that participation in exercise training programs which consisted of moderate intensity aerobic exercise had beneficial effects on autonomic function, as indicated by increases in HRR as well as HRV parameters. Since both slow HRR and attenuated HRV predict adverse health outcomes in patients with CHF, optimal exercise prescription should not only aim to improve exercise capacity but also focus on autonomic function in patients with CHF. Physical training could be considered as an alternative approach for autonomic dysfunction in patients with CHF.

The ability of heart rate to recover after exercise is related to the capacity of the cardiovascular system mediated by vagal activity and baroreceptor adaptations that occur during exercise [9]. HRR can be an additional indicator of outcome measures and risk stratification in patients undergoing cardiac rehabilitation [23]. This systematic review showed that moderate-intensity aerobic exercise training was effective in improving HRR, especially HRR_2. It was reported that HRR_1 is considered a marker of cardiac parasympathetic outflow, and HRR_2 is thought to be related to the gradual withdrawal of sympathetic activity [39]. Both parameters are of considerable importance to cardiac patients. However, HRR_2 was reported to be superior to all other time periods as a mortality predictor [40].

The magnitude of improvement of HRR seemed to be associated with the improvements in fitness levels of the patients [24]. Several studies have reported that changes in HRR were attributed to a greater heart rate reserve after training [23, 41] but do not negate the potential influence of training on autonomic balance. An increase in vagal tone after training is implied by the reduction in resting heart rate, and the higher peak heart rate suggests enhanced sympathetic drive, lowered vagal influence, or both at peak exertion during exercise. These all indicated exercise training provided a benefit to autonomic control.

Reduced HRV in patients with CHF is often thought to be related to neurohormonal activation and attenuation of cardiac vagal tone [5, 16]. Different HRV assessment contexts (e.g., short-term versus 24-hour recordings) seemed to have some influences on the results. The effect of exercise training was likely to be more prominent in the studies utilizing a short-term resting ECG recording in our included trials. The time domain HRV parameters reflect overall autonomic modulation with parasympathetic components well represented by the RMSSD and pNN50 parameter. In frequency domain HRV analysis, it is generally accepted that the HF is reflective of parasympathetic activity, while the LF reflects both sympathetic and parasympathetic activity and is now believed to represent baroreflex sensitivity instead of sympathetic modulation [42, 43]. Sympathovagal balance is frequently described by LF/HF ratio. Recently, LF/HF ratio represents a relationship between baroreflex sensitivity and vagal modulation rather than sympathovagal balance [44]. There is no HRV parameter reflecting directly sympathetic activation modulation. The results of this review revealed that exercise training has considerable effects on HRV in patients with CHF, including increase in vagal tone and modulation of sympathovagal balance activity.

Two out of the 8 RCTs employed resistance exercise and 6 trials employed moderate-intensity aerobic exercise training. Most of these results showed positive exercise training effect on the autonomic nervous system regulation in CHF. Only one trial did not show the effect of HRV after exercise consisting of resistance training in these trials [30]. Therefore, moderate intensity aerobic training is currently evidenced as the main adjunct in improving autonomous regulatory function in CHF. However, there were different studies addressing the effects of different intensities of aerobic exercise on autonomic function in CHF. Dimopoulos and colleagues [31] conducted a study to compare the effects of moderate intensity continuous exercise and high intensity interval exercise (100% peak work rate for 30 s and alternating with rest for 30 s) training on HRR_1 in patients with CHF. This study was not eligible for inclusion because they did not include a real control group. There were 24 stable CHF patients who completed a rehabilitation program of 36 sessions, three times per week. The results showed that moderate intensity continuous exercise rather than high intensity interval exercise training improved early HRR_1. Future studies should pay more attention to the issues about optimal exercise intensity. On the other hand, more studies are required to investigate the effects of resistance exercise training in this population.

In addition to exercise intensity, the training duration would be the other possible factors affecting the effects of exercise program for autonomic function. The mean follow-up duration in our included clinical trials was relatively short (ranging from 12 to 24 weeks). A longer follow-up duration after exercise training might amount to some contrasting effects on HRV and HRR since it has been suggested that CHF patients may require more time to achieve modulation of autonomic tone and responsiveness [24, 45].

Due to a great variability of evaluation tools and analytical methodology across trials, direct comparison and pooling of the data was restricted. We calculated the effect sizes of some of the included RCTs, but not all, because some trials did not report the detail data. Generally, the studies eligible for inclusion into our systematic review showed that exercise training improved autonomic function within moderate effect sizes ranging from 0.49 [24] to 0.70 [27]. More studies with larger effect sizes are needed to provide better evidence.

The mechanisms by which exercise improves autonomic function are not well understood. Some mediators are considered to play a role in increasing cardiac vagal tone in response to exercise training [46, 47]. Nitric oxide (NO) is thought to have an effect on cardiac vagal tone and sympathetic influence; on the other side, angiotensin II is a known inhibitor of cardiac vagal activity. Exercise training has been shown to improve NO bioavailability and lower angiotensin II levels [46, 47]. In addition, recent studies have shown that chronic inflammation affected the autonomic nervous system [48]. Interleukin-6 may affect autonomic balance by disturbing the hypothalamic-pituitary-adrenal axis at the level of the pituitary and adrenal glands [49]. The anti-inflammatory effects of exercise training might be a possible mechanism by which exercise improves autonomic function. Nevertheless, future studies are needed to explore this issue.

5. Limitations

The systematic review combined the results of different studies; nevertheless, several limitations in generalizing the findings must be acknowledged. First, a relatively small number of trials, all of which included a relatively small sample size, were examined. Second, trials reported in languages other than English and Chinese were excluded, as were trials reported only as abstracts. These exclusions may have led to publication bias. Third, considerable variations in the parameters analyzed and the HRV assessment contexts (e.g., short-term versus long-term recordings of HRV) all restricted direct comparisons of the data and pooled analysis. Finally, the exercise modes, intensity, and duration varied among trials that hindered determination of the optimal exercise prescription parameters on HRR and HRV.

6. Implications and Recommendations for Future Study

According to the results of this systematic review, moderate-intensity aerobic training utilizing walking or bicycle ergometer in 50–80% of heart rate reserve, 30 minutes to 1 hour, 3 to 5 times per week for at least 12 weeks may be recommended for amelioration of the autonomic regulation in people with CHF. Further research could examine additional aspects of the effects of exercise training in this population, for example, the impact on the responses to exercise training under different levels of severity and the underlying causes of CHF. A threshold intensity or amount of exercise may be needed to affect cardiac autonomic function. The type of the exercise, such as high-intensity interval aerobic training or resistance training, may also influence the obtained effects.

7. Conclusion

HRR and HRV analysis provide noninvasive indicators to reveal the changes in the autonomic nervous system at rest and in response to physical activity in patients with CHF. This systematic review indicated that participation in exercise training has beneficial effects on ameliorating autonomic dysfunction in people with CHF. Large-scale, well-controlled, and longitudinal studies are needed to provide more evidence and further examine mechanisms that underlie the links between the effects of exercise training and autonomic function in CHF.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] V. L. Roger, A. S. Go, D. M. Lloyd-Jones et al., "Heart disease and stroke statistics—2012 update: a report from the American Heart Association," *Circulation*, vol. 125, no. 1, pp. e2–e220, 2012.

[2] S. A. Hunt, D. W. Baker, M. H. Chin et al., "ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure)," *Circulation*, vol. 104, no. 24, pp. 2996–3007, 2001.

[3] S. H. Kubo, T. S. Rector, A. J. Bank, R. E. Williams, and S. M. Heifetz, "Endothelium-dependent vasodilation is attenuated in patients with heart failure," *Circulation*, vol. 84, no. 4, pp. 1589–1596, 1991.

[4] S. Adamopoulos, J. T. Parissis, and D. T. Kremastinos, "New aspects for the role of physical training in the management of patients with chronic heart failure," *International Journal of Cardiology*, vol. 90, no. 1, pp. 1–14, 2003.

[5] M. G. Kienzle, D. W. Ferguson, C. L. Birkett, G. A. Myers, W. J. Berg, and D. J. Mariano, "Clinical, hemodynamic and sympathetic neural correlates of heart rate variability in congestive heart failure," *The American Journal of Cardiology*, vol. 69, no. 8, pp. 761–767, 1992.

[6] M. A. Samara and W. H. W. Tang, "Heart failure with systolic dysfunction," in *Manual of Cardiovascular Medicine*, B. P. Griffin, T. D. Callahan, V. Menon et al., Eds., p. 148, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 2013.

[7] E. O. Nishime, C. R. Cole, E. H. Blackstone, F. J. Pashkow, and M. S. Lauer, "Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG," *The Journal of the American Medical Association*, vol. 284, no. 11, pp. 1392–1398, 2000.

[8] J. V. Freeman, F. E. Dewey, D. M. Hadley, J. Myers, and V. F. Froelicher, "Autonomic nervous system interaction with the cardiovascular system during exercise," *Progress in Cardiovascular Diseases*, vol. 48, no. 5, pp. 342–362, 2006.

[9] K. Imai, H. Sato, M. Hori et al., "Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 24, no. 6, pp. 1529–1535, 1994.

[10] C. R. Cole, E. H. Blackstone, F. J. Pashkow, C. E. Snader, and M. S. Lauer, "Heart rate recovery immediately after exercise as a predictor of mortality," *The New England Journal of Medicine*, vol. 341, no. 18, pp. 1351–1357, 1999.

[11] R. Arena, M. Guazzi, J. Myers, and M. A. Peberdy, "Prognostic value of heart rate recovery in patients with heart failure," *American Heart Journal*, vol. 151, no. 4, pp. 851.e7–851.e13, 2006.

[12] S. Y. Jae, E. S. Ahn, K. S. Heffernan et al., "Relation of heart rate recovery after exercise to C-reactive protein and white blood cell count," *The American Journal of Cardiology*, vol. 99, no. 5, pp. 707–710, 2007.

[13] Task Force European Society Cardiology of the of North American Society Pacing the of Electrophysiology, "Heart rate variability: standards of measurement, physiological interpretation, and clinical use," *Circulation*, vol. 93, no. 5, pp. 1043–1065, 1996.

[14] R. J. Sheppard, N. Racine, A. Roof, A. Ducharme, M. Blanchet, and M. White, "Heart rate recovery—a potential marker of clinical outcomes in heart failure patients receiving beta-blocker therapy," *Canadian Journal of Cardiology*, vol. 23, no. 14, pp. 1135–1138, 2007.

[15] J. J. Goldberger, F. K. Le, M. Lahiri, P. J. Kannankeril, J. Ng, and A. H. Kadish, "Assessment of parasympathetic reactivation after exercise," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 290, no. 6, pp. H2446–H2452, 2006.

[16] J. Nolan, P. D. Batin, R. Andrews et al., "Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-Heart)," *Circulation*, vol. 98, no. 15, pp. 1510–1516, 1998.

[17] M. Dörr and M. Halle, "Exercise training as a key component of heart failure therapy," *Herz*, vol. 40, no. 2, pp. 206–214, 2015.

[18] F. Edelmann, G. Gelbrich, H.-D. Dngen et al., "Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study," *Journal of the American College of Cardiology*, vol. 58, no. 17, pp. 1780–1791, 2011.

[19] B. A. F. van Tol, R. J. Huijsmans, D. W. Kroon, M. Schothorst, and G. Kwakkel, "Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis," *European Journal of Heart Failure*, vol. 8, no. 8, pp. 841–850, 2006.

[20] E. J. Davies, T. Moxham, K. Rees et al., "Exercise Training for systolic heart failure: cochrane systematic review and meta-analysis," *European Journal of Heart Failure*, vol. 12, no. 7, pp. 706–715, 2010.

[21] E. M. Dixon, M. V. Kamath, N. McCartney, and E. L. Fallen, "Neural regulation of heart rate variability in endurance athletes and sedentary controls," *Cardiovascular Research*, vol. 26, no. 7, pp. 713–719, 1992.

[22] G. R. H. Sandercock, R. Grocott-Mason, and D. A. Brodie, "Changes in short-term measures of heart rate variability after eight weeks of cardiac rehabilitation," *Clinical Autonomic Research*, vol. 17, no. 1, pp. 39–45, 2007.

[23] J. Myers, D. Hadley, U. Oswald et al., "Effects of exercise training on heart rate recovery in patients with chronic heart failure," *American Heart Journal*, vol. 153, no. 6, pp. 1056–1063, 2007.

[24] Y. T. Yaylali, G. Fındıkoglu, M. Yurtdas, S. Konukcu, and H. Senol, "The effects of baseline heart rate recovery normality and exercise training protocol on heart rate recovery in patients with

heart failure," *The Anatolian Journal of Cardiology*, vol. 15, no. 9, pp. 727–734, 2015.

[25] S. E. Selig, M. F. Carey, D. G. Menzies et al., "Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow," *Journal of Cardiac Failure*, vol. 10, no. 1, pp. 21–30, 2004.

[26] K. Murad, P. H. Brubaker, D. M. Fitzgerald et al., "Exercise training improves heart rate variability in older patients with heart failure: a randomized, controlled, single-blinded trial," *Congestive Heart Failure*, vol. 18, no. 4, pp. 192–197, 2012.

[27] R. Ricca-Mallada, E. R. Migliaro, J. Piskorski, and P. Guzik, "Exercise training slows down heart rate and improves deceleration and acceleration capacity in patients with heart failure," *Journal of Electrocardiology*, vol. 45, no. 3, pp. 214–219, 2012.

[28] K. Kiilavuori, L. Toivonen, H. Näveri, and H. Leinonen, "Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability," *European Heart Journal*, vol. 16, no. 4, pp. 490–495, 1995.

[29] G. Y. Yeh, P. M. Wayne, and R. S. Phillips, "Tai Chi exercise in patients with chronic heart failure," *Medicine and Sport Science*, vol. 52, pp. 195–208, 2008.

[30] Å. Cider, H. Tygesson, M. Hedberg, L. Seligman, B. Wennerblom, and K. S. Sunnerhagen, "Peripheral muscle training in patients with clinical signs of heart failure," *Scandinavian Journal of Rehabilitation Medicine*, vol. 29, no. 2, pp. 121–127, 1997.

[31] S. Dimopoulos, M. Anastasiou-Nana, D. Sakellariou et al., "Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure," *European Journal of Cardiovascular Prevention & Rehabilitation*, vol. 13, no. 1, pp. 67–73, 2006.

[32] F. Iellamo, V. Manzi, G. Caminiti et al., "Dose-response relationship of baroreflex sensitivity and heart rate variability to individually-tailored exercise training in patients with heart failure," *International Journal of Cardiology*, vol. 166, no. 2, pp. 334–339, 2013.

[33] P. Koufaki, T. H. Mercer, K. P. George, and J. Nolan, "Low-volume high-intensity interval training vs. continuous aerobic cycling in patients with chronic heart failure: a pragmatic randomised clinical trial of feasibility and effectiveness," *Journal of Rehabilitation Medicine*, vol. 46, no. 4, pp. 348–356, 2014.

[34] P. Dobšák, J. Tomandl, L. Spinarova et al., "Effects of neuromuscular electrical stimulation and aerobic exercise training on arterial stiffness and autonomic functions in patients with chronic heart failure," *Artificial Organs*, vol. 36, no. 10, pp. 920–930, 2012.

[35] A. I. Larsen, K. Gjesdal, C. Hall, P. Aukrust, T. Aarsland, and K. Dickstein, "Effect of exercise training in patients with heart failure: a pilot study on autonomic balance assessed by heart rate variability," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 11, no. 2, pp. 162–167, 2004.

[36] M. Pietilä, K. Malminiemi, R. Vesalainen et al., "Exercise training in chronic heart failure: beneficial effects on cardiac ^{11}C-hydroxyephedrine PET, autonomic nervous control, and ventricular repolarization," *Journal of Nuclear Medicine*, vol. 43, no. 6, pp. 773–779, 2002.

[37] S. Adamopoulos, P. Ponikowski, E. Cerquetani et al., "Circadian pattern of heart rate variability in chronic heart failure patients: effects of physical training," *European Heart Journal*, vol. 16, no. 10, pp. 1380–1386, 1995.

[38] A. Radaelli, A. J. S. Coats, S. Leuzzi et al., "Physical training enhances sympathetic and parasympathetic control of heart rate and peripheral vessels in chronic heart failure," *Clinical Science*, vol. 91, supplement 1, pp. 92–94, 1996.

[39] M. Buchheit, Y. Papelier, P. B. Laursen, and S. Ahmaidi, "Noninvasive assessment of cardiac parasympathetic function: postexercise heart rate recovery or heart rate variability?" *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 293, no. 1, pp. H8–H10, 2007.

[40] K. Shetler, R. Marcus, V. F. Froelicher et al., "Heart rate recovery: validation and methodologic issues," *Journal of the American College of Cardiology*, vol. 38, no. 7, pp. 1980–1987, 2001.

[41] M. Y. Desai, E. De la Peña-Almaguer,, and F. Mannting, "Abnormal heart rate recovery after exercise as a reflection of an abnormal chronotropic response," *The American Journal of Cardiology*, vol. 87, no. 10, pp. 1164–1169, 2001.

[42] M. T. La Rovere, J. T. Bigger Jr., F. I. Marcus, A. Mortara, and P. J. Schwartz, "Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction," *The Lancet*, vol. 351, no. 9101, pp. 478–484, 1998.

[43] J. P. Moak, D. S. Goldstein, B. A. Eldadah et al., "Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation," *Heart Rhythm*, vol. 4, no. 12, pp. 1523–1529, 2007.

[44] I. Cygankiewicz and W. Zareba, "Heart rate variability," *Handbook of Clinical Neurology*, vol. 117, no. 3, pp. 379–393, 2013.

[45] F. S. Routledge, T. S. Campbell, J. A. McFetridge-Durdle, and S. L. Bacon, "Improvements in heart rate variability with exercise therapy," *Canadian Journal of Cardiology*, vol. 26, no. 6, pp. 303–312, 2010.

[46] B. A. Kingwell, "Nitric oxide as a metabolic regulator during exercise: effects of training in health and disease," *Clinical and Experimental Pharmacology and Physiology*, vol. 27, no. 4, pp. 239–250, 2000.

[47] J. N. Townend, M. Al-Ani, J. N. West, W. A. Littler, and J. H. Coote, "Modulation of cardiac autonomic control in humans by angiotensin II," *Hypertension*, vol. 25, no. 6, pp. 1270–1275, 1995.

[48] E. Jüttler, V. Tarabin, and M. Schwaninger, "Interleukin-6 (IL-6): a possible neuromodulator induced by neuronal activity," *Neuroscientist*, vol. 8, no. 3, pp. 268–275, 2002.

[49] M. C. Ruzek, A. H. Miller, S. M. Opal, B. D. Pearce, and C. A. Biron, "Characterization of early cytokine responses and an interleukin (IL)-6-dependent pathway of endogenous glucocorticoid induction during murine cytomegalovirus infection," *The Journal of Experimental Medicine*, vol. 185, no. 7, pp. 1185–1192, 1997.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 596367, 10 pages
http://dx.doi.org/10.1155/2015/596367

Review Article

Effects of Light Intensity Activity on CVD Risk Factors: A Systematic Review of Intervention Studies

Romeo B. Batacan Jr.,[1,2] Mitch J. Duncan,[3] Vincent J. Dalbo,[1,4] Patrick S. Tucker,[1,4] and Andrew S. Fenning[1,2]

[1] *Institute for Health and Social Science Research, Central Queensland University, Bruce Highway, Rockhampton, QLD 4702, Australia*
[2] *Centre for Physical Activity Studies, Central Queensland University, Bruce Highway, Rockhampton, QLD 4702, Australia*
[3] *School of Medicine & Public Health, Priority Research Centre for Physical Activity and Nutrition, Faculty of Health and Medicine, The University of Newcastle, University Drive, Callaghan, NSW 2308, Australia*
[4] *Clinical Biochemistry Laboratory, Central Queensland University, Bruce Highway, Rockhampton, QLD 4702, Australia*

Correspondence should be addressed to Romeo B. Batacan Jr.; r.j.batacan@cqu.edu.au

Received 22 May 2015; Revised 13 September 2015; Accepted 20 September 2015

Academic Editor: Antonio Crisafulli

The effects of light intensity physical activity (LIPA) on cardiovascular disease (CVD) risk factors remain to be established. This review summarizes the effects of LIPA on CVD risk factors and CVD-related markers in adults. A systematic search of four electronic databases (PubMed, Academic Search Complete, SPORTDiscus, and CINAHL) examining LIPA and CVD risk factors (body composition, blood pressure, glucose, insulin, glycosylated hemoglobin, and lipid profile) and CVD-related markers (maximal oxygen uptake, heart rate, C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and tumor necrosis factor receptors 1 and 2) published between 1970 and 2015 was performed on 15 March 2015. A total of 33 intervention studies examining the effect of LIPA on CVD risk factors and markers were included in this review. Results indicated that LIPA did not improve CVD risk factors and CVD-related markers in healthy individuals. LIPA was found to improve systolic and diastolic blood pressure in physically inactive populations with a medical condition. Reviewed studies show little support for the role of LIPA to reduce CVD risk factors. Many of the included studies were of low to fair study quality and used low doses of LIPA. Further studies are needed to establish the value of LIPA in reducing CVD risk.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide [1]. Several biological risk factors, such as male gender, family history of heart disease, high blood pressure (BP), dyslipidemia, obesity, glucose abnormalities, insulin resistance, and lifestyle risk factors, such as smoking, poor diet, lack of physical activity, low cardiorespiratory fitness, excessive alcohol use, and stress, are associated with the development and progression of CVD [2, 3]. Notably, these lifestyle risk factors strongly influence the established biological CVD risk factors and also affect novel pathways of risk such as inflammation [4]. For instance, physical activity and cardiorespiratory fitness (measured by maximal oxygen consumption (VO_2 max) and heart rate (HR)) are known to improve a number of traditional biological risk factors for CVD, including BP [5], high-density lipoprotein (HDL) cholesterol [6], body fat [7], and novel risk factors such as C-reactive protein (CRP) levels [8].

There is excellent evidence that physical activity, particularly moderate-to-vigorous intensity physical activity (MVPA), is effective in the prevention and treatment of CVD [9, 10]. The existing public health guidelines emphasize participation in MVPA to achieve health benefits [9, 10]. However, the view that physical activity has to be moderate to vigorous to achieve cardiovascular risk reduction has been questioned [11]. It is suggested that physical activity performed at light intensity level can also provide health benefits [12, 13]. As such, although early studies demonstrate that light intensity physical activity (LIPA) (20 < 40% VO_2 max [14])

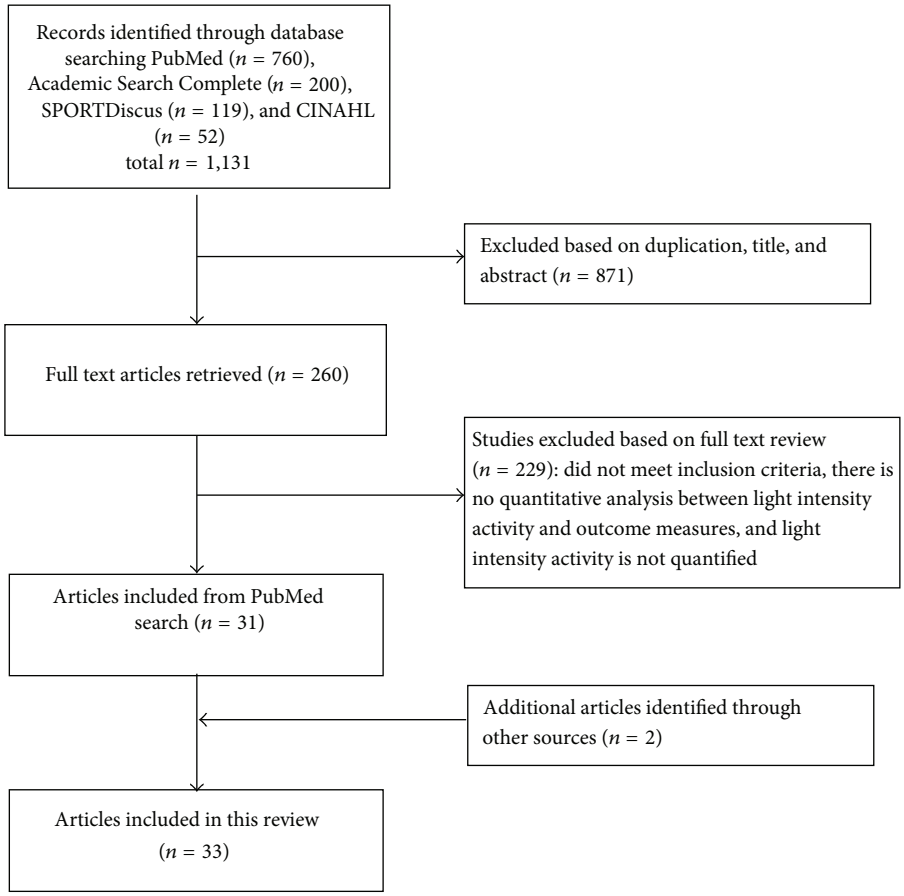


Figure 1: Flow diagram of study selection.

is not associated with reduced CVD and overall mortality rates [15, 16], there is growing recognition of the potential for LIPA to reduce disease risk, particularly CVD [17]. This is emphasized by cross-sectional studies demonstrating that LIPA is associated with CVD risk factors [12, 13, 18]. LIPA is important to understand, from a health perspective, as adults tend to spend a greater portion of their day (6.5 hr/day [13, 14]) performing LIPA compared to MVPA (0.7 hr/day [13, 14]). Many people often find it more attractive and attainable to perform LIPA than MVPA (40 < 85% VO_2 max) [19]. Furthermore, recent evidence suggests that muscle fiber recruitment during LIPA may potentially produce cellular signals which may regulate risk factors for disease [20].

As a result, clarifying the role of LIPA in CVD prevention is important given the amount of time people spend engaged in light intensity activities and its potential as an intervention target. To date, there has been no comprehensive review of literature describing the role of LIPA on CVD risk factors. Therefore, the aim of this review is to systematically examine the effects of LIPA on CVD risk factors (body composition, BP, glucose, insulin, glycosylated hemoglobin, total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglycerides) and other CVD-related markers (VO_2 max, HR, CRP, interleukin-6, tumor necrosis factor- (TNF-) alpha, TNF receptor 1 (TNFR1), and TNF receptor 2 (TNFR2)) in adults.

2. Methods

A systematic search was performed on 15 March 2015 according to PRISMA guidelines [21]. Articles were retrieved from PubMed, Academic Search Complete, SPORTDiscus, and CINAHL using multiple search criteria provided in Supplementary Table 1 in Supplementary Material available online at http://dx.doi.org/10.1155/2015/596367. Initially, titles and abstracts of identified articles were checked for relevance by two reviewers (RB and PT). Subsequently, both reviewers independently reviewed the full text of potentially eligible papers. Any disagreement between the two reviewers for inclusion was resolved through discussion. Additional articles were identified via hand-searching and reviewing the reference lists of relevant papers. Figure 1 presents the flow of papers through the study selection process.

Studies were considered to be eligible for inclusion based on the following criteria: (i) participants were ≥ 18 years of age; (ii) the study examined at least one of the following CVD risk factors/markers in humans: body mass, body mass index (BMI), waist circumference (WC), hip circumference, waist-to-hip ratio (WHR), % body fat, HR, BP, VO_2 max, glucose (fasting or postprandial), glycosylated hemoglobin, insulin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, CRP, interleukin-6, TNF-alpha, TNF receptor 1, or TNF receptor 2 levels; (iii) the study reported

an intervention (both randomized and nonrandomized) that imposed on participants a single or periodic bouts of LIPA defined as activities between 1.6 < 3.0 METs, 20 < 40% VO_2 max, and 20 < 40% heart rate reserve (HRR) or the relative intensity of 40 < 55% HR max [14, 22]; (iv) the study included quantitative analysis (statistical comparison of intervention to baseline or a control group) of the effect of LIPA on at least one of the outcome measures; (v) the study was published or accepted for publication in refereed journals from 1970 up to and including the search date; (vi) the study was published in the English language. Due to the lack of a standardized definition of LIPA for resistance training, only aerobic/flexibility exercises were included in the study.

Two authors (RB and PT) independently assessed the quality of the studies that met the inclusion criteria (Table 1). The risk of bias and strength of evidence from individual studies were assessed using Downs and Black Checklist [23], allowing for the assessment of the methodological quality of randomized controlled trials and nonrandomized studies of health care interventions. This 27-point checklist assesses the strength of reporting, external validity, internal validity, and statistical power. As some questions are worth more than one point, the maximum score that can be received is 32. Adapted from another systematic review [24], the score obtained by each study was divided by 32 and multiplied by 100 to provide a "study quality percentage." Study quality percentages were then classified as high (66.7% or higher), fair (between 50.0 and 66.6%), and low (less than 50.0%) [24].

Following data extraction, the interventions included in this review were heterogeneous in terms of the type, frequency, and duration of physical activities, as well as body mass, physical fitness, and dietary intake of the participants. Thus, meta-analyses or pooling of data across studies would be inappropriate so a qualitative synthesis of the evidence was performed instead.

A modified form of coding system described by Sallis et al. [25] was used to summarize the effect of LIPA on CVD risk factors/markers. If 0–33% of the studies reported a statistically significant difference between LIPA and CVD risk factors/markers, the result was categorized as no effect (0). If 34–59% of the studies reported a statistically significant difference, the result was categorized as inconsistent (?). If 60–100% of the studies reported a statistically significant difference, the result was rated as positive (+) or negative (−), respective of the direction of the effect. When four or more studies supported a difference or no difference, it was coded as ++, −−, or 00 to indicate consistent observations. The ?? code indicated a marker that has been examined in four or more studies with inconsistent findings (e.g., out of 5 studies, 3 indicated a significant positive effect and 2 indicated a significant negative effect).

Results were then stratified by health status of the population (healthy or those with a medical condition). Studies in which participant physical activity was less than 150 min/wk of moderate intensity physical activity or 75 min/wk of vigorous intensity physical activity or participants were not engaged in regular physical activity/exercise (as described in the primary study) or participants were defined as sedentary were subsequently classified as "physically inactive" and the results are summarized separately for these studies.

3. Results

General study characteristics are summarized in Table 1; more detailed study characteristics are presented in Supplementary Table 2. All studies had LIPA intervention with the number of study participants in the LIPA group ranging from $n = 6$–39. Participants were primarily young, adult, and males (18–39 years old). Duration of LIPA interventions ranged from an acute bout of training lasting 5 minutes to chronic training lasting 30 min per session, 3 times per week, for 9 months. The exercise modalities involved stretching and calisthenics ($n = 1$), hand rim wheelchair training ($n = 1$), yoga ($n = 1$), standing ($n = 2$), slow flexibility exercises ($n = 3$), stationary cycling ($n = 7$), and slow home/outdoor or treadmill walking ($n = 18$). Fifteen [26–40] of the 33 reviewed studies had participants classified as overweight or obese and 7 studies [31, 33, 34, 36, 41–43] consisted of participants suffering from medical conditions (hypertension, diabetes mellitus, chronic heart failure, gestational diabetes, colorectal cancer, metabolic syndrome, and HIV infection).

Studies included in this review were assigned a quality rating. The study quality was rated low in 11 studies, fair in 20 studies, and high in 2 studies. Over 90% of the studies scored 1 point for defining study objectives, describing exposure and outcome variables, utilizing random sampling of the target population, providing data sources, and describing the data collection process. Seventeen studies (51%) [26, 34, 36, 39, 42, 44–55] did not describe participant recruitment methods and 10 studies (30%) [26, 40, 44, 46–52] did not report inclusion criteria. Five studies (15%) [33, 34, 41, 56] did not report compliance rates. Of the studies that reported compliance, compliance was generally good with participants completing 81% to 100% of the activity sessions implemented per study design. Six studies [26, 31, 35, 38–40] reported power calculations relevant to their study aims. All but 4 studies [26, 30, 31, 33] performed the activity sessions in a laboratory/clinic directly supervised by a research staff. Those not conducted in the laboratory, light intensity activity was performed outdoors/at home with participants monitoring their own HR.

A summary table of the effect of LIPA on CVD risk factors and markers can be found in Table 2; the effects of LIPA on CVD risk factors/markers reported in each study are presented in Supplementary Table 3. Results demonstrated LIPA training interventions to have no significant effect on markers of body composition in physically inactive or healthy, with a medical condition, adults. All studies that examined the effect of LIPA on body mass [26, 29, 35, 53], WC [31, 32, 35, 41], BMI [26, 31, 32, 41], and % body fat [30, 32] reported no significant change. LIPA was found to have no effect on systolic or diastolic BP in healthy adults while improvements in BP were found in physically inactive populations with a medical condition. Three [31, 32, 39] of 9 studies (33%) reported significant decreases in systolic BP while 2 [31, 39] of 9 studies (22%) reported significant decreases in diastolic BP.

Table 1: Summary of included studies, sorted by disease status and duration of intervention.

Study reference	Disease status[c]	Duration of intervention	Weight status (based on mean BMI)	Study design	Sample size N = LIPA group (total)	Age range (mean ± SD)	Baseline activity level[c]	Modality of intervention	Downs and Black Score	Study quality
[56]	No	9 mo	No data	RCT	33 (72)	60–81 (63.9 ± 3.9)	No data	Laboratory-based	17	Fair
[26][a]	No	24 wk	Overweight	RCT	12 (36)	18–45	Sedentary	Free-living	16	Fair
[30]	No	16 wk	Obese	RCT	6 (25)	(52.8 ± 7.2)	Sedentary	Free-living	19	Fair
[28]	No	16 wk	Overweight	RCT	17 (51)	20–50	Sedentary	Laboratory-based	19	Fair
[27]	No	16 wk	Overweight	RCT	17 (51)	20–50	Sedentary	Laboratory-based	19	Fair
[29]	No	16 wk	Overweight	RCT	17 (51)	20–50	Sedentary	Laboratory-based	19	Fair
[53]	No	12 wk	No data	NRCT	10 (26)	(25 ± 2.5)	No exercise habit	Laboratory-based	15	Low
[32]	No	10 wk	Overweight	RCD	39	≥55	Sedentary	Laboratory-based	21	Fair
[55]	No	7 wk	No data	RCT	9 (24)	18–30	Untrained	Laboratory-based	17	Fair
[35]	No	5 d	Overweight	RCD	23	35–65 (48.2 ± 7.9)	Sedentary	Laboratory-based	21	Fair
[57][b]	No	4 d	Normal	RCD	18	(21 ± 2)	Physically inactive	Laboratory-based	18	Fair
[63][a]	No	~238 min	No data	RCD	13	(23.8 ± 0.9)	Physically active	Laboratory-based	19	Fair
[54][b]	No	~214.5 min	Normal	RCD	9	(24.0 ± 4.0)	Recreationally active	Laboratory-based	17	Fair
[49][a]	No	120 min	No data	RCD	12	(25.8 ± 1.2)	Regular physical activity	Laboratory-based	14	Low
[50]	No	120 min	Normal	Case series	22	18–23	Regular structured running	Laboratory-based	13	Low
[44]	No	120 min	No data	RCD	6	(25 ± 2)	Moderately trained	Laboratory-based	15	Low
[47][a]	No	90 min	Normal	RCD	12	(29.5 ± 6.2 male; 24.3 ± 1.4 female)	Recreationally active	Laboratory-based	15	Low
[46]	No	90 min	No data	RCD	12	(28.2 ± 1.5)	Recreationally active	Laboratory-based	15	Low
[51]	No	45 min	Normal	URCT	22	(23.22 ± 2.88)	Runners (<5 miles/wk)	Laboratory-based	15	Low
[37]	No	40 min	Overweight	RCD	12	(46.2 ± 1.1)	Sedentary	Laboratory-based	20	Fair
[45]	No	35 min	Normal	RCD	14	(25.4 ± 1.8)	Endurance trained	Laboratory-based	16	Fair
[40][b]	No	28 min	Overweight	RCD	10	(24 ± 3)	No data	Laboratory-based	18	Fair
[38][b]	No	28 min	Obese	RCD	19	45–65	Physically inactive	Laboratory-based	24	High
[39][b]	No	28 min	Obese	RCD	19	45–65	Physically inactive	Laboratory-based	22	High
[52]	No	15 min	Normal	RCD	6	22–39 (32 ± 4)	Athletes	Laboratory-based	15	Low
[48]	No	5 min	No data	RCD	6	(23.5 ± 0.9)	Sedentary	Laboratory-based	14	Low
[31]	HPN	12 wk	Obese	RCT	20 (40)	45–65	Sedentary	Free-living	20	Fair
[41]	DM2	12 wk	No data	RCT	29 (59)	(60 ± 10)	No data	Laboratory-based	14	Low
[42]	CHF	8 wk	No data	RCT	7 (21)	(58 ± 3)	Habitually active	Laboratory-based	16	Fair
[33]	GDM	6 wk	Obese	Case control	10 (30)	(33.4 ± 3.3)	No data	Free-living	16	Fair
[34]	Colon Cancer	2 wk	Overweight	RCT	10 (23)	59–67	No data	Laboratory-based	14	Low
[36][a]	MS	≈103 min	Obese	RCD	14	(43 ± 9)	Physically inactive	Laboratory-based	16	Fair
[43]	HIV infected	60 min	No data	RCT	11 (38)	(42.9 ± 7.5)	Exercise-naive	Laboratory-based	18	Fair

BMI: body mass index; DM2: diabetes mellitus type 2; GDM: gestational diabetes mellitus; HIV: human immunodeficiency virus; HPN: hypertension; LIPA: light intensity physical activity; min: minute; mo: month; MS: metabolic syndrome; NRCT: nonrandomized controlled trial; RCD: randomized cross-over design; RCT: randomized controlled trial; URCT: uncontrolled randomized clinical trial; wk: week. Physical inactivity is defined as not meeting at least 150 minutes of moderate intensity physical activity or 75 minutes of vigorous intensity physical activity. [a]Compared to a control group with no prescribed activity. [b]Compared to a sitting group. [c]Disease status and baseline activity level (using the terminology of the primary study) presented were as per inclusion criteria.

Table 2: Summary of studies examining the effect of LIPA on CVD risk factors and CVD-related markers.

Marker	Summary coding of studies involving physically inactive population		Summary coding of studies involving populations with a medical condition		Summary coding of studies involving healthy population		Summary coding of all included studies	
CVD risk factors	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]
Body mass	0/4 (0%)	No (00)	0/0 (0%)	NA	0/4 (0%)	No (00)	0/5 (0%)	No (00)
WC	0/3 (0%)	No (0)	0/2 (0%)	No (0)	0/0 (0%)	NA	0/4 (0%)	No (00)
BMI	0/3 (0%)	No (0)	0/2 (0%)	No (0)	0/0 (0%)	NA	0/4 (0%)	No (00)
% BF	0/2 (0%)	No (0)	0/0 (0%)	NA	0/0 (0%)	NA	0/2 (0%)	No (0)
Systolic BP	3/5 (60%)	Positive (++)	2/3 (67%)	Positive (+)	0/5 (0%)	No (00)	3/9 (33%)	No (00)
Diastolic BP	2/5 (40%)	Inconsistent (??)	2/3 (67%)	Positive (+)	0/5 (0%)	No (00)	2/9 (22%)	No (00)
Glucose	1/8 (12%)	No (00)	1/3 (33%)	No (0)	0/8 (0%)	No (00)	3/16 (19%)	No (00)
Insulin	1/8 (12%)	No (00)	0/1 (0%)	NA	0/8 (0%)	No (00)	1/13 (8%)	No (00)
Hba1C	0/1 (0%)	NA	0/1 (0%)	NA	0/0 (0%)	NA	0/2 (0%)	No (0)
Total cholesterol	1/5 (20%)	No (00)	0/0 (0%)	NA	1/6 (17%)	No (00)	2/11(18%)	No (00)
HDL cholesterol	0/7 (0%)	No (00)	0/1 (0%)	NA	1/8 (12%)	No (00)	1/13 (8%)	No (00)
LDL cholesterol	0/4 (0%)	No (00)	0/0 (0%)	NA	0/3 (0%)	No (0)	0/6 (0%)	No (00)
Triglycerides	2/8 (25%)	No (00)	0/1 (0%)	NA	4/7 (57%)	Inconsistent (??)	5/13 (38%)	Inconsistent (??)
CVD-related markers	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]	n/N (%)[a,b,c]	Effect (0/−/+/?)[d]
VO_2 max	2/5 (40%)	Inconsistent (??)	0/1 (0%)	NA	1/2 (50%)	Inconsistent (?)	3/8 (38%)	Inconsistent (??)
Resting HR	1/4 (25%)	No (00)	0/1 (0%)	NA	0/3 (0%)	No (0)	1/5 (20%)	No (00)
CRP	0/2 (0%)	No (0)	0/0 (0%)	NA	0/0 (0%)	NA	0/2 (0%)	No (0)
Interleukin-6	0/3 (0%)	No (0)	0/2 (0%)	No (0%)	0/0 (0%)	NA	0/4 (0%)	No (00)
TNF-alpha	0/1 (0%)	NA	0/1 (0%)	NA	0/0 (0%)	NA	0/2 (0%)	No (0)

[a] n = number of studies reporting difference in the expected direction.

[b] N = number of identified studies of interest.

[c] (%) = percentage of studies reporting differences in the expected direction.

[d] Summary effect. No effect (0): 0–33% of studies reported significant differences; inconsistent (?): 34–59% of studies reported significant differences; positive (+) or negative (−) effect: 60–100% of studies demonstrated significant differences; ≥4 studies: positive (++), negative (−−), no effect (00), and inconsistent findings (??).

CVD markers (waist-to-hip ratio, heart rate maximal, and tumor necrosis factor receptor 2) with only one study demonstrating the effect of light intensity activity were excluded in this summary table.

BF: body fat; BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; CVD: cardiovascular disease; Hba1c: glycosylated hemoglobin; HDL: high-density lipoprotein; HR: heart rate; LDL; low-intensity lipoprotein; NA: not applicable; TNF: tumor necrosis factor; VO_2 max: maximal oxygen uptake; WC: waist circumference.

LIPA was found to have no effect on glucose and insulin response in physically inactive or healthy, with a medical condition, adults. Three [33, 38, 40] of 16 studies (19%) reported significant decreases in glucose and 1 of 13 (8%) reported significant decrease in insulin level. When the effect of LIPA on blood lipid markers was examined, no significant changes were found for total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides in physically inactive or healthy individuals and inconsistent findings on triglycerides in healthy adults. One [50] of 11 studies (9%) reported a significant increase in total cholesterol while 2 [26, 46] of 11 studies (18%) reported significant decreases in total cholesterol. One [50] of 13 studies (8%) reported a significant increase in HDL cholesterol, 5 [36, 46, 49, 54, 57] of 13 studies (38%) reported significant increases in triglycerides, and 0 of 6 studies (0%) reported an effect on LDL cholesterol.

Regarding other CVD-related markers, the effect of LIPA on VO_2 max is inconclusive in physically inactive or healthy adults. Three [27, 32, 56] of 8 studies (38%) reported significant increases in VO_2 max. LIPA was also found to have no effect on resting HR in physically inactive or healthy adults. One [32] of 5 studies (20%) reported a significant reduction in resting HR. All studies that examined the effect of LIPA on CRP [30, 37], interleukin-6 [30, 34, 37, 43], and TNF-alpha [30, 34] reported no significant effect in physically inactive, with a medical condition, adults.

4. Discussion

The effect of LIPA on markers of cardiovascular risk factors was systematically reviewed. LIPA resulted in no significant improvements in body composition, glucose, insulin

(in physically inactive or healthy, with a medical condition, adults), total cholesterol, HDL cholesterol, LDL cholesterol (in physically inactive or healthy adults), or triglycerides (in physically inactive adults) and inconsistent findings on triglycerides in healthy adults. On the other hand, LIPA was found to improve systolic and diastolic BP in physically inactive populations with a medical condition. Additionally, when examining CVD-related markers, we found inconsistent results regarding the effect of LIPA on VO_2 max in physically inactive or healthy adults, no significant changes on resting HR in physically inactive or healthy adults, and no significant changes on inflammatory markers in physically inactive or with a medical condition adults.

Nine studies [26, 29–32, 35, 41, 53, 55] examined the effect of LIPA on body composition and found no effect in either physically inactive or healthy, with a medical condition, populations. One study concluded that LIPA performed 30 min, 8 times a day, for 5 days, did not result in any significant change on body mass and WC [35]. The rest of the studies demonstrated that LIPA performed 30–90 min, 3 to 5 times per wk, for ≥7 wk, did not result in any significant effect on body mass [26, 29, 53, 55], WC [31, 32, 41], BMI [26, 31, 32, 41], WHR [26], or % body fat [30, 32]. This result is consistent with previous research findings that conclude at least 250 min/wk of moderate intensity (≥3 METs) training is needed if the primary purpose of the training program is to elicit reductions in body mass and fat mass [58, 59]. There are no recommended durations of LIPA required to elicit weight loss; however, the amount of LIPA required to improve body composition is likely to be much greater than that required for MVPA given the reduced intensity level. Physical activity alone if greater than 250 min/wk without caloric restriction has a limited influence on body composition [27, 28, 60] and may only cause 1–3% change in body mass and adipose tissue [61]. In addition, evidence suggests that the total volume of physical activity is a key factor in achieving weight loss [62]. An individual intending to lose weight through physical activity without dietary restriction would need to engage in a large volume (26 MET-hr per wk) of physical activity to achieve a 5% weight reduction [62]. In most studies to date, the volume of LIPA used is less (<10.5 MET-hr per wk) than the 26 MET-hr per wk that may be required to improve body composition.

Findings of this review also indicate no significant changes in resting BP in healthy adults but found significant improvements in physically inactive individuals with a medical condition. Participants who followed a single bout (15 min) [52] and periodic bouts (2 min every 20 min over 5 hr period) [40] of treadmill walking, and long term (30–60 min 3–5x/wk, ≥10 wk) LIPA [30, 32, 41, 53, 56] demonstrated no significant changes in resting BP. Two studies [31, 32] reported a decrease in systolic BP and one study reported [31] a decrease in diastolic BP following ≥ 10 wk of walking [31] and a combination of treadmill walking, stationary cycling and stepping [32]. In both studies, the improved BP response was found in physically inactive participants with hypertension. Similarly, in prehypertensive and hypertensive physically inactive, obese adults, one study [39] with a different study design (randomized cross-over study breaking up prolonged sitting with LIPA breaks) found significant reductions in systolic and diastolic BP in individuals interrupting sitting time with light intensity walking relative to individuals with uninterrupted sitting. Thus, LIPA appears unlikely to influence the BP response in normotensive populations but may be able to provide an effect in hypertensive, physically inactive populations.

There were no significant improvements in glucose and insulin response following LIPA in either physically inactive or healthy, with a medical condition, adults. All 6 studies [36, 44, 45, 47, 49, 63] reported no effects of glucose and insulin response during a single bout (35–237.5 min) of LIPA. Following periodic bouts (214.5 ± 28 min divided in 9 bouts, 30–60 min 3x/wk, 30 min 8x/day, 4 hr walking, and 2 hr standing/day) of LIPA, 7 [30, 32, 35, 41, 53, 54, 57] of 10 studies reported no significant changes in glucose and 6 [30, 32, 35, 53, 54, 57] of 7 studies reported no significant changes in insulin. These results are consistent with epidemiological data showing no significant association between fasting glucose and time spent performing LIPA (5.7–6.0 hr/day) (but not with 2 hr plasma glucose which was found to be significantly associated with LIPA) [12, 13]. In contrast, 2 studies [38, 40] reported a decrease in postprandial glucose (and insulin [38]) after interrupting sitting with light intensity standing/walking. These laboratory-based studies compared a light intensity standing/walking group to a sitting group, employed LIPA (14 sessions of 2 min LIPA separated by 20 min sitting period) dispersed throughout the day, and measured postprandial glucose. These findings were validated in a recent meta-analysis that found significant reductions in blood glucose postprandial response and insulin levels after interrupting sedentary periods with LIPA breaks [64]. Another study [33] with a longer, structured, light intensity walking intervention period (120–160 min/wk walking for 6 wk) also demonstrated reductions in capillary glucose concentrations post-intervention compared to baseline. This study used obese women with gestational diabetes. In summary, there is no consistent intervention evidence to support improved glucose metabolism with LIPA in healthy adults. Studies [33, 38, 40] suggesting that LIPA may improve glucose and insulin response examined individuals with higher glucose baseline values or compared LIPA to a sedentary (sitting) group or used multiple bouts of LIPA dispersed throughout the day. Thus, there may be some evidence to support the view that LIPA influences glucose and insulin metabolism, but this evidence appears to be limited to individuals (1) with impaired cardiometabolic function or (2) who are compared to no activity (sedentary) control groups.

Most studies in this review reported no significant change in total cholesterol [30, 32, 40, 47, 49, 51, 53, 57], HDL cholesterol [26, 30, 32, 36, 40, 46, 47, 49, 51, 53, 57, 63], LDL cholesterol [26, 30, 32, 46, 51, 57], in physically inactive or healthy individuals, or in triglycerides [26, 30, 32, 35, 40, 51, 53, 63] in physically inactive adults following LIPA. Inconsistent findings were found on the effect of LIPA on triglycerides in healthy adults. This result is not consistent with evidence from epidemiological studies demonstrating a beneficial association of larger volumes of LIPA with HDL cholesterol (4.3 hr/day of LIPA) [65] and triglycerides

(5.7–6.0 hr/day; <150 min/wk MVPA, but LIPA exceeded sedentary behavior) [18, 66]. Conversely, similar results were found in a recent meta-analysis that reported no significant reductions in triglycerides after interrupting sedentary periods with LIPA breaks [64]. These conflicting results reported in the literature in regard to the effect of LIPA in blood lipid markers may be due to differences in study protocol and participants' baseline lipid levels.

In this review, 5 [36, 46, 49, 54, 57] of 10 studies demonstrated significant reductions in triglycerides following LIPA in healthy adults. These studies used short intervention periods (≤4 days) of light intensity walking and 3 studies [36, 49, 54] used a high fat test meal prior to blood sampling. This immediate lowering of serum triglycerides following LIPA is most likely due to enhanced triglyceride peripheral tissue uptake of serum triglycerides that result from exercise-induced activity of lipoprotein lipase, the rate limiting enzyme for the hydrolysis of triglyceride-rich lipoproteins [67]. The increased activity of lipoprotein lipase (persisting up to 18 hr) following muscular contractions causes an increase in the removal of triglycerides from the circulation [68]. Unfortunately, none of these studies explored whether or not triglyceride reductions persisted for more than 24 hr following LIPA bout.

VO_2 max, resting HR, and inflammatory markers that are known to impact CVD risk factors were also examined. LIPA had inconsistent results in regard to the effects on VO_2 max and no effect on resting HR in physically inactive or healthy adults. Studies employing long term (≥8 wk) LIPA protocols generally reported no change [28–30, 42, 48, 53, 56], while others reported improvement in VO_2 max [27, 32, 56] and HR [32]. It is possible that certain types of aerobic exercise may lead to health-related benefits and yet may not be of sufficient quantity or quality to improve VO_2 max or decrease resting HR [69]. Despres and Lamarche [70] proposed that prolonged (exact duration not specified) low intensity (approximately 50% VO_2 max) endurance exercise performed 45–60 min on an almost daily basis significantly improved insulin sensitivity and lipoprotein metabolism through mechanisms that are likely to be independent of the training-related changes in cardiorespiratory fitness. The proposed mechanisms included the net increase in energy expenditure and losses in total body fat and abdominal adipose tissue which contributed to improved carbohydrate and lipid metabolism [70]. This hypothesis, however, remains to be established. At present, only 3 [27, 32, 56] of 7 studies reported a positive effect on VO_2 max; 2 [27, 32] of these 3 studies examined physically inactive, overweight adults. The third study [56] neglected to report baseline physical activity and BMI. Thus, the beneficial effects of LIPA, in regard to adaptations to VO_2 max, are equivocal and may be most pronounced in individuals with low levels of physical activity [71, 72] suggesting that the benefits of LIPA on VO_2 max may be limited to populations who are least active.

No significant changes in inflammatory markers (CRP, interleukin-6, and TNF-alpha) were found in physically inactive or with a medical condition participants engaging in a single bout (40–60 min) [37, 43], periodic bouts (40 min/day for two wk) [34], or long term (30 min 3x/wk for 16 wk) [30] LIPA. Research in this area is limited and more studies are needed to clarify the effect of LIPA on inflammatory markers. Results from the interventions (3 out of 4 studies) included in this review demonstrate that acute effects are unlikely to occur and future research should seek to examine changes in inflammatory markers following participation in LIPA over longer time periods.

This review provides consistent evidence that LIPA is not effective at improving CVD risk factors and other CVD-related health markers in apparently healthy individuals. Some evidence surfaced suggesting that LIPA may improve markers of CVD risk factors (BP) in physically inactive adults with a medical condition. These findings provide some support to cross-sectional studies suggesting that LIPA may be beneficial in elderly, physically inactive, with a medical condition, individuals [65, 73, 74]. However, due to limited intervention studies available that have examined these cohorts of individuals, it is difficult to make conclusions with full certainty. Future studies should attempt to elucidate the effects of LIPA in elderly, physically inactive, with a medical condition, adults. Since LIPA is low intensity and appears to be most practical in physically inactive populations, daily LIPA and MVPA of participants should be accounted for in future work.

The dose of LIPA used in the reviewed studies was modest in comparison to the volume of LIPA typically performed by individuals (e.g., ≤150 min/wk which equates to <10.5 MET-hr per wk). Therefore, future studies are encouraged to use greater doses (much higher than the recommended 150 min/wk moderate intensity physical activity due to the reduced intensity level of LIPA) to assist in clarifying the role of LIPA to elicit positive changes in CVD risk factors and CVD-related markers.

5. Conclusions

Although cross-sectional research findings [12, 13, 18] suggest that LIPA may help to improve an individual's metabolic profile, there is no evidence to support the effect of LIPA in providing positive changes in CVD risk factors in healthy adults. Little intervention evidence was found to support the positive effect of LIPA in CVD risk factors in physically inactive adults with a medical condition. In particular, significant improvements in BP following LIPA were achieved by physically inactive, hypertensive individuals [31, 32, 39]. However, it should be noted that many studies reviewed did not control, either statistically or by design, for potential confounding variables such as controlling for accumulated MVPA or monitoring dietary intake. Most of the studies have also used small doses of LIPA (<10.5 MET-hr per wk). Given that adults spend a considerable proportion of their day (6.5 hr/day [13, 14]) performing LIPA, it may be possible that this volume of LIPA is not enough of a stimulus to promote favorable adaptations in the examined biological markers of CVD risk. Aside from increasing the volume, it may also be worthwhile to examine the effects of LIPA dispersed throughout the day similar to recent studies [35, 38–40] that have used regular short bouts of LIPA to interrupt prolonged

periods of sitting. This may be useful as recent meta-analysis found these breaks in sitting to be associated with improved glucose and insulin response [64]. In summary, there may be some evidence to support the view that LIPA influences some CVD risk factors in certain populations, but more well-designed experiments with greater control of confounding factors are required to confirm this.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

R. B. Batacan is supported by the Strategic Research Scholarship grant from Central Queensland University. This paper is in part supported by CQUniversity Health Collaborative Research Network. Mitch J. Duncan is supported by a Future Leader Fellowship (ID 100029) from the National Heart Foundation of Australia.

References

[1] WHO, *Global Status Report on Noncommunicable Diseases 2010*, World Health Organization, Geneva, Switzerland, 2011.

[2] D. S. Prasad, Z. Kabir, A. K. Dash, and B. C. Das, "Cardiovascular risk factors in developing countries: a review of clinico-epidemiological evidence," *CVD Prevention and Control*, vol. 5, no. 4, pp. 115–123, 2010.

[3] M. R. Carnethon, S. S. Gidding, R. Nehgme, S. Sidney, D. R. Jacobs Jr., and K. Liu, "Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors," *The Journal of the American Medical Association*, vol. 290, no. 23, pp. 3092–3100, 2003.

[4] D. Mozaffarian, P. W. F. Wilson, and W. B. Kannel, "Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease," *Circulation*, vol. 117, no. 23, pp. 3031–3038, 2008.

[5] S. P. Whelton, A. Chin, X. Xin, and J. He, "Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials," *Annals of Internal Medicine*, vol. 136, no. 7, pp. 493–503, 2002.

[6] J. L. Durstine, P. W. Grandjean, P. G. Davis, M. A. Ferguson, N. L. Alderson, and K. D. DuBose, "Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis," *Sports Medicine*, vol. 31, no. 15, pp. 1033–1062, 2001.

[7] S. L. Wong, P. T. Katzmarzyk, M. Z. Nichaman, T. S. Church, S. N. Blair, and R. Ross, "Cardiorespiratory fitness is associated with lower abdominal fat independent of body mass index," *Medicine and Science in Sports and Exercise*, vol. 36, no. 2, pp. 286–291, 2004.

[8] D. Aronson, R. Sella, M. Sheikh-Ahmad et al., "The association between cardiorespiratory fitness and C-reactive protein in subjects with the metabolic syndrome," *Journal of the American College of Cardiology*, vol. 44, no. 10, pp. 2003–2007, 2004.

[9] P. D. Thompson, D. Buchner, I. L. Piña et al., "Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity)," *Circulation*, vol. 107, no. 24, pp. 3109–3116, 2003.

[10] G. A. Gaesser, "Exercise for prevention and treatment of cardiovascular disease, type 2 diabetes, and metabolic syndrome," *Current Diabetes Reports*, vol. 7, no. 1, pp. 14–19, 2007.

[11] S. G. Wannamethee and A. G. Shaper, "Physical activity in the prevention of cardiovascular disease: an epidemiological perspective," *Sports Medicine*, vol. 31, no. 2, pp. 101–114, 2001.

[12] G. N. Healy, D. W. Dunstan, J. Salmon, E. Cerin, J. E. Shaw, and N. Owen, "Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose," *Diabetes Care*, vol. 30, no. 6, pp. 1384–1389, 2007.

[13] G. N. Healy, K. Wijndaele, D. W. Dunstan, J. E. Shaw, J. Salmon, and N. Owen, "Objectively measured sedentary time, physical activity, and metabolic risk the Australian Diabetes, Obesity and Lifestyle Study (AusDiab)," *Diabetes Care*, vol. 31, no. 2, pp. 369–371, 2008.

[14] K. Norton, L. Norton, and D. Sadgrove, "Position statement on physical activity and exercise intensity terminology," *Journal of Science and Medicine in Sport*, vol. 13, no. 5, pp. 496–502, 2010.

[15] I.-M. Lee and R. S. Paffenbarger Jr., "Associations of light, moderate, and vigorous intensity physical activity with longevity: the Harvard Alumni Health Study," *American Journal of Epidemiology*, vol. 151, no. 3, pp. 293–299, 2000.

[16] S. Yu, J. W. G. Yarnell, P. M. Sweetnam, and L. Murray, "What level of physical activity protects against premature cardiovascular death? The Caerphilly study," *Heart*, vol. 89, no. 5, pp. 502–506, 2003.

[17] J. A. Levine, "Non-exercise activity thermogenesis (NEAT)," *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 16, no. 4, pp. 679–702, 2002.

[18] G. N. Healy, D. W. Dunstan, J. E. Shaw, P. Z. Zimmet, and N. Owen, "Objectively measured sedentary time and light-intensity physical activity are independently associated with components of the metabolic syndrome: the AusDiab study," *Diabetologia*, vol. 50, supplement 1, pp. S67–S68, 2007.

[19] R. K. Dishman and J. Buckworth, "Increasing physical activity: a quantitative synthesis," *Medicine and Science in Sports and Exercise*, vol. 28, no. 6, pp. 706–719, 1996.

[20] M. T. Hamilton, D. G. Hamilton, and T. W. Zderic, "Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease," *Diabetes*, vol. 56, no. 11, pp. 2655–2667, 2007.

[21] A. Liberati, D. G. Altman, J. Tetzlaff et al., "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration," *British Medical Journal*, vol. 339, Article ID b2700, 2009.

[22] B. E. Ainsworth, W. L. Haskell, M. C. Whitt et al., "Compendium of physical activities: an update of activity codes and MET intensities," *Medicine and Science in Sports and Exercise*, vol. 32, supplement 9, pp. S498–S504, 2000.

[23] S. H. Downs and N. Black, "The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions," *Journal of Epidemiology and Community Health*, vol. 52, no. 6, pp. 377–384, 1998.

[24] S. A. Newell, J. A. Bowman, and J. D. Cockburn, "Can compliance with nonpharmacologic treatments for cardiovascular disease be improved?" *American Journal of Preventive Medicine*, vol. 18, no. 3, pp. 253–261, 2000.

[25] J. F. Sallis, J. J. Prochaska, and W. C. Taylor, "A review of correlates of physical activity of children and adolescents," *Medicine and Science in Sports and Exercise*, vol. 32, no. 5, pp. 963–975, 2000.

[26] C. Keller and R. P. Treviño, "Effects of two frequencies of walking on cardiovascular risk factor reduction in Mexican American women," *Research in Nursing and Health*, vol. 24, no. 5, pp. 390–401, 2001.

[27] K. L. Cox, V. Burke, A. R. Morton, L. J. Beilin, and I. B. Puddey, "The independent and combined effects of 16 weeks of vigorous exercise and energy restriction on body mass and composition in free-living overweight men—a randomized controlled trial," *Metabolism: Clinical and Experimental*, vol. 52, no. 1, pp. 107–115, 2003.

[28] K. L. Cox, V. Burke, A. R. Morton, L. J. Beilin, and I. B. Puddey, "Independent and additive effects of energy restriction and exercise on glucose and insulin concentrations in sedentary overweight men," *The American Journal of Clinical Nutrition*, vol. 80, no. 2, pp. 308–316, 2004.

[29] K. L. Cox, I. B. Puddey, A. R. Morton, V. Burke, L. J. Beilin, and M. McAleer, "Exercise and weight control in sedentary overweight men: effects on clinic and ambulatory blood pressure," *Journal of Hypertension*, vol. 14, no. 6, pp. 779–790, 1996.

[30] M. Krause, J. Rodrigues-Krause, C. O'Hagan et al., "The effects of aerobic exercise training at two different intensities in obesity and type 2 diabetes: implications for oxidative stress, low-grade inflammation and nitric oxide production," *European Journal of Applied Physiology*, vol. 114, no. 2, pp. 251–260, 2014.

[31] C. L. Goldie, C. A. Brown, S. M. J. Hains, J. L. Parlow, and R. Birtwhistle, "Synergistic effects of low-intensity exercise conditioning and β-blockade on cardiovascular and autonomic adaptation in pre- and postmenopausal women with hypertension," *Biological Research for Nursing*, vol. 15, no. 4, pp. 433–442, 2013.

[32] V. A. Cornelissen, J. Arnout, P. Holvoet, and R. H. Fagard, "Influence of exercise at lower and higher intensity on blood pressure and cardiovascular risk factors at older age," *Journal of Hypertension*, vol. 27, no. 4, pp. 753–762, 2009.

[33] M. H. Davenport, M. F. Mottola, R. McManus, and R. Gratton, "A walking intervention improves capillary glucose control in women with gestational diabetes mellitus: a pilot study," *Applied Physiology, Nutrition, and Metabolism*, vol. 33, no. 3, pp. 511–517, 2008.

[34] H. Allgayer, S. Nicolaus, and S. Schreiber, "Decreased interleukin-1 receptor antagonist response following moderate exercise in patients with colorectal carcinoma after primary treatment," *Cancer Detection and Prevention*, vol. 28, no. 3, pp. 208–213, 2004.

[35] A. A. Thorp, B. A. Kingwell, P. Sethi, L. Hammond, N. Owen, and D. W. Dunstan, "Alternating bouts of sitting and standing attenuate postprandial glucose responses," *Medicine and Science in Sports and Exercise*, vol. 46, no. 11, pp. 2053–2061, 2014.

[36] M. L. Mestek, E. P. Plaisance, L. A. Ratcliff, J. K. Taylor, S.-O. Wee, and P. W. Grandjean, "Aerobic exercise and postprandial lipemia in men with the metabolic syndrome," *Medicine and Science in Sports and Exercise*, vol. 40, no. 12, pp. 2105–2111, 2008.

[37] A. E. Mendham, C. E. Donges, E. A. Liberts, and R. Duffield, "Effects of mode and intensity on the acute exercise-induced IL-6 and CRP responses in a sedentary, overweight population," *European Journal of Applied Physiology*, vol. 111, no. 6, pp. 1035–1045, 2011.

[38] D. W. Dunstan, B. A. Kingwell, R. Larsen et al., "Breaking up prolonged sitting reduces postprandial glucose and insulin responses," *Diabetes Care*, vol. 35, no. 5, pp. 976–983, 2012.

[39] R. N. Larsen, B. A. Kingwell, P. Sethi, E. Cerin, N. Owen, and D. W. Dunstan, "Breaking up prolonged sitting reduces resting blood pressure in overweight/obese adults," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 24, no. 9, pp. 976–982, 2014.

[40] D. P. Bailey and C. D. Locke, "Breaking up prolonged sitting with light-intensity walking improves postprandial glycemia, but breaking up sitting with standing does not," *Journal of Science and Medicine in Sport*, vol. 18, no. 3, pp. 294–298, 2014.

[41] L. Skoro-Kondza, S. S. Tai, R. Gadelrab, D. Drincevic, and T. Greenhalgh, "Community based yoga classes for type 2 diabetes: an exploratory randomised controlled trial," *BMC Health Services Research*, vol. 9, article 33, 8 pages, 2009.

[42] A. Gordon, R. Tyni-Lenné, H. Persson, L. Kaijser, E. Hultman, and C. Sylvén, "Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure," *Clinical Cardiology*, vol. 19, no. 7, pp. 568–574, 1996.

[43] W. D. Dudgeon, K. D. Phillips, J. L. Durstine et al., "Individual exercise sessions alter circulating hormones and cytokines in HIV-infected men," *Applied Physiology, Nutrition, and Metabolism*, vol. 35, no. 4, pp. 560–568, 2010.

[44] J. F. Horowitz, R. Mora-Rodriguez, L. O. Byerley, and E. F. Coyle, "Substrate metabolism when subjects are fed carbohydrate during exercise," *The American Journal of Physiology—Endocrinology and Metabolism*, vol. 276, no. 5, pp. E828–E835, 1999.

[45] T. Fujimoto, J. Kemppainen, K. K. Kalliokoski, P. Nuutila, M. Ito, and J. Knuuti, "Skeletal muscle glucose uptake response to exercise in trained and untrained men," *Medicine and Science in Sports and Exercise*, vol. 35, no. 5, pp. 777–783, 2003.

[46] N. V. Tsetsonis and A. E. Hardman, "The influence of the intensity of treadmill walking upon changes in lipid and lipoprotein variables in healthy adults," *European Journal of Applied Physiology and Occupational Physiology*, vol. 70, no. 4, pp. 329–336, 1995.

[47] N. V. Tsetsonis, "Effects of low and moderate intensity treadmill walking on postprandial lipaemia in healthy young adults," *European Journal of Applied Physiology and Occupational Physiology*, vol. 73, no. 5, pp. 419–426, 1996.

[48] R. Perini, C. Orizio, A. Comande, M. Castellano, M. Beschi, and A. Veicsteinas, "Plasma norepinephrine and heart rate dynamics during recovery from submaximal exercise in man," *European Journal of Applied Physiology and Occupational Physiology*, vol. 58, no. 8, pp. 879–883, 1989.

[49] H. E. Aldred, I. C. Perry, and A. E. Hardman, "The effect of a single bout of brisk walking on postprandial lipemia in normolipidemic young adults," *Metabolism*, vol. 43, no. 7, pp. 836–841, 1994.

[50] H. E. Pay, A. E. Hardman, G. J. W. Jones, and A. Hudson, "The acute effects of low-intensity exercise on plasma lipids in endurance-trained and untrained young adults," *European Journal of Applied Physiology and Occupational Physiology*, vol. 64, no. 2, pp. 182–186, 1992.

[51] R. A. Hughes, W. G. Thorland, T. Eyford, and T. Hood, "The acute effects of exercise duration on serum lipoprotein metabolism," *The Journal of Sports Medicine and Physical Fitness*, vol. 30, no. 1, pp. 37–44, 1990.

[52] G. A. Wittert, D. E. Stewart, M. P. Graves et al., "Plasma corticotrophin releasing factor and vasopressin responses to

exercise in normal man," *Clinical Endocrinology*, vol. 35, no. 4, pp. 311–317, 1991.

[53] C. Goto, Y. Higashi, M. Kimura et al., "Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress," *Circulation*, vol. 108, no. 5, pp. 530–535, 2003.

[54] I.-Y. Kim, S. Park, J. R. Trombold, and E. F. Coyle, "Effects of moderate- and intermittent low-intensity exercise on Postprandial Lipemia," *Medicine and Science in Sports and Exercise*, vol. 46, no. 10, pp. 1882–1890, 2014.

[55] R. Van Den Berg, S. De Groot, K. M. A. Swart, and L. H. V. Van Der Woude, "Physical capacity after 7 weeks of low-intensity wheelchair training," *Disability & Rehabilitation*, vol. 32, no. 26, pp. 2244–2252, 2010.

[56] J. S. Stevenson and R. Topp, "Effects of moderate and low intensity long-term exercise by older adults," *Research in Nursing & Health*, vol. 13, no. 4, pp. 209–218, 1990.

[57] B. M. F. M. Duvivier, N. C. Schaper, M. A. Bremers et al., "Minimal intensity physical activity (standing and walking) of longer duration improves insulin action and plasma lipids more than shorter periods of moderate to vigorous exercise (cycling) in sedentary subjects when energy expenditure is comparable," *PLoS ONE*, vol. 8, no. 2, Article ID e55542, 2013.

[58] American College of Sports Medicine, "Proper and improper weight loss programs," *Medicine and Science in Sports and Exercise*, vol. 15, no. 1, pp. 9–13, 1983.

[59] M. L. Stefanick, "Exercise and weight control," *Exercise and Sport Sciences Reviews*, vol. 21, pp. 363–396, 1993.

[60] J.-P. Despres and B. Lamarche, "Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease," *Nutrition Research Reviews*, vol. 6, no. 1, pp. 137–159, 1993.

[61] J. W. Rankin, "Effective diet and exercise interventions to improve body composition in obese individuals," *American Journal of Lifestyle Medicine*, vol. 9, no. 1, pp. 48–62, 2015.

[62] H. Kohl and T. Murray, *Foundations of Physical Activity and Public Health*, Human Kinetics, 2012.

[63] C. S. Katsanos, P. W. Grandjean, and R. J. Moffatt, "Effects of low and moderate exercise intensity on postprandial lipemia and postheparin plasma lipoprotein lipase activity in physically active men," *Journal of Applied Physiology*, vol. 96, no. 1, pp. 181–188, 2004.

[64] S. F. M. Chastin, T. Egerton, C. Leask, and E. Stamatakis, "Meta-analysis of the relationship between breaks in sedentary behavior and cardiometabolic health," *Obesity*, vol. 23, no. 9, pp. 1800–1810, 2015.

[65] J. Kim, K. Tanabe, N. Yokoyama, H. Zempo, and S. Kuno, "Objectively measured light-intensity lifestyle activity and sedentary time are independently associated with metabolic syndrome: a cross-sectional study of Japanese adults," *International Journal of Behavioral Nutrition and Physical Activity*, vol. 10, article 30, 2013.

[66] P. D. Loprinzi, H. Lee, and B. J. Cardinal, "Daily movement patterns and biological markers among adults in the United States," *Preventive Medicine*, vol. 60, pp. 128–130, 2014.

[67] R. H. Eckel, "Lipoprotein lipase: a multifunctional enzyme relevant to common metabolic diseases," *The New England Journal of Medicine*, vol. 320, no. 16, pp. 1060–1068, 1989.

[68] M. A. Kantor, E. M. Cullinane, P. N. Herbert, and P. D. Thompson, "Acute increase in lipoprotein lipase following prolonged exercise," *Metabolism: Clinical and Experimental*, vol. 33, no. 5, pp. 454–457, 1984.

[69] M. L. Pollock, G. A. Gaesser, J. D. Butcher et al., "The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults," *Medicine and Science in Sports and Exercise*, vol. 30, no. 6, pp. 975–991, 1998.

[70] J.-P. Despres and B. Lamarche, "Low-intensity endurance exercise training, plasma lipoproteins and the risk of coronary heart disease," *Journal of Internal Medicine*, vol. 236, no. 1, pp. 7–22, 1994.

[71] U. Ekelund, H. A. Ward, T. Norat et al., "Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC)," *The American Journal of Clinical Nutrition*, vol. 101, no. 3, pp. 613–621, 2015.

[72] G. E. Duncan, M. G. Perri, D. W. Theriaque, A. D. Hutson, R. H. Eckel, and P. W. Stacpoole, "Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults," *Diabetes Care*, vol. 26, no. 3, pp. 557–562, 2003.

[73] G. N. Healy, E. A. Winkler, C. L. Brakenridge, M. M. Reeves, E. G. Eakin, and M. Alemany, "Accelerometer-derived sedentary and physical activity time in overweight/obese adults with type 2 diabetes: cross-sectional associations with cardiometabolic biomarkers," *PLOS ONE*, vol. 10, no. 3, Article ID e0119140, 2015.

[74] P. D. Loprinzi, H. Lee, and B. J. Cardinal, "Evidence to support including lifestyle light-intensity recommendations in physical activity guidelines for older adults," *American Journal of Health Promotion*, vol. 29, no. 5, pp. 277–284, 2015.