

WJC 6th Anniversary Special Issues (1): Hypertension

Exercise training in hypertension: Role of microRNAs

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Author contributions: Neves VJ, Fernandes T, Roque FR, Soci UP, Melo SFS wrote part of manuscript; Neves VJ was organizer; Oliveira EM, adviser, edited this manuscript.

Supported by Grants from Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP, No. 2009/18370-3 and 2010/50048-1; by Conselho Nacional de Desenvolvimento Científico e Tecnológico-CNPq, No. 476515/2012-2, USP/PRP-NAPmiR; by the grant from FAPESP, No. 2012/04104-2, No. 2013/10472-7 and No. 2010/09438-0; and by the grant from CNPq, No. 159827/2011-6, No. 159827/2011-6 and No. 308267/2013-3

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Received: December 29, 2013 Revised: March 25, 2014

Accepted: May 29, 2014

Published online: August 26, 2014

Abstract

Hypertension is a complex disease that constitutes an important public health problem and demands many studies in order to understand the molecular mechanisms involving its pathophysiology. Therefore, an increasing number of studies have been conducted and new therapies are continually being discovered. In this context, exercise training has emerged as an important non-pharmacological therapy to treat hypertensive patients, minimizing the side effects of pharmacological therapies and frequently contributing to allow pharmacotherapy to be suspended. Several mechanisms have been associated with the pathogenesis of hypertension, such as hyperactivity of the sympathetic nervous system and renin-angiotensin aldosterone system,

impaired endothelial nitric oxide production, increased oxygen-reactive species, vascular thickening and stiffening, cardiac hypertrophy, impaired angiogenesis, and sometimes genetic predisposition. With the advent of microRNAs (miRNAs), new insights have been added to the perspectives for the treatment of this disease, and exercise training has been shown to be able to modulate the miRNAs associated with it. Elucidation of the relationship between exercise training and miRNAs in the pathogenesis of hypertension is fundamental in order to understand how exercise modulates the cardiovascular system at genetic level. This can be promising even for the development of new drugs. This article is a review of how exercise training acts on hypertension by means of specific miRNAs in the heart, vascular system, and skeletal muscle.

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Key words: Exercise training; Hypertension; MicroRNA; Heart; Vascular system; Macrocirculation; Microcirculation; Muscles; Angiogenesis

Core tip: Numerous studies have shown that exercise training exerts beneficial effects on hypertension. Thus, several important studies have established links between exercise training, hypertension and the post-transcriptional regulators known as miRNAs. It is interesting to note that exercise training helps to control hypertension through these regulators, by promoting changes in the cardiovascular system towards normality. This review summarizes the way in which exercise training acts on the cardiovascular system to control the side effects of hypertension on the heart, macro- and microcirculation, and skeletal muscles.

Neves VJ, Fernandes T, Roque FR, Soci UP, Melo SFS, Oliveira EM. Exercise training in hypertension: Role of microRNAs. *World J Cardiol* 2014; 6(8): 713-727 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i8/713.htm> DOI:

INTRODUCTION

Exercise training (ET) is a well-known form of preventing or reducing cardiovascular disturbances. It is able to prevent or reduces the vascular changes that are the precursors of high blood pressure, such as diminished nitric oxide (NO) availability and increased oxidative stress. It is also able to reduce sympathetic nervous system (SNS) activity and cardiac output, improve angiogenesis and reduce peripheral vascular resistance. Therefore, ET has been used as a most successful non-pharmacological therapy for the treatment of hypertensive patients. It promotes a reduction in blood pressure and helps to reduce the medication used by these patients (in some cases, it promotes discontinuation of the medication used); thereby decreasing the side effects of pharmacotherapy and the financial cost of hypertension to public health^[1]. Despite the continuous advances in options of pharmacological therapies for hypertension, it remains an important and growing public health problem worldwide, affecting more than one billion people across the planet^[2]. Today, it is estimated that it kills nine million people per year^[3]. It is in this context that ET has a high relevance in hypertension, contributing as an additional tool for the treatment or prevention of this disease.

Hypertension is a persistent elevation of systemic blood pressure with multifactorial causes. Its development is determined by a cluster of environmental factors associated with genetic susceptibility. The mechanisms by which hypertension is generated (such as hyperactivity of SNS, overactivation of the renin-angiotensin-aldosterone system, endothelial dysfunction, and others) are responsible for the gradual development of pathological manifestations in the form of vascular, cardiac and renal diseases, such as atherosclerosis, stroke, pathological cardiac hypertrophy, myocardial infarction, heart and kidney failure^[2]. Whereas, ET is able to minimize the effects of multiple factors that induce the development of hypertension, and by extension, it also helps to prevent or reduce the development of the aforementioned pathological manifestations.

ET promotes numerous cardiovascular and muscular adjustments that are antihypertensive. These adjustments depend on the amount of ET, which is determined by the volume (training time), intensity (degree of training load) and frequency of ET (number of training sessions at any given time)^[4]. In this context, aerobic exercise promotes physiological cardiac hypertrophy^[5], reduction in systolic blood pressure (SBP) and heart rate (both at rest and under submaximal loads)^[6,7], increases the lumen diameter of the coronary arteries^[8] and cardiac blood flow^[9], increases the circulating NO^[10], corrects the peripheral capillary rarefaction in hypertensive animals^[7], promotes revascularization^[11] and reduces peripheral vascular resistance. ET also promotes important meta-

bolic adaptations that reflect on blood pressure control, for example, reduction of plasma triglycerides and low-density lipoproteins, as well as increased insulin sensitivity in tissues^[12]. In addition to aerobic exercise, physical resistance training with anaerobic characteristics is also able to induce physiological cardiac hypertrophy^[13,14]. Moreover, positive effects have been shown on reducing systolic, mean, and diastolic blood pressure, and heart rate in trained when compared with untrained rats^[14].

It is interesting to note that aerobic or resistance training may promote different adaptations in the cardiovascular system, but all adaptations are beneficial to regulating the blood pressure. However it is not only the type (aerobic or anaerobic) of exercise that is important, but also the modality of exercise performed (for example running, walking, cycling and swimming)^[15]. In this case, Nualnim *et al*^[16] has shown that swimming training was able to promote hypotensive effects and improve the vascular function in adults over 50 years of age. Cycling exercise (30 min, 5 d per week, for 3 mo) significantly decreased the resting blood pressure and increased the NO plasma concentration in older (59-69 years) normotensive women, suggesting that aerobic ET exerts the beneficial effect of increasing NO production in previously sedentary older humans^[10]. Furthermore, moderate intensity walking decreased the baseline SBP of postmenopausal women with hypertension^[17], and treadmill exercise improved the endothelial function and vascular stiffness in coronary and mesenteric arteries of spontaneously hypertensive rats, which may be related to decreased oxidative stress and increased endothelial-dependent NO production^[15].

In view of the beneficial effects of ET on the treatment of hypertension, and the new genetic findings revealed in the last decades, several scientists have turned their attention to a new class of gene expression regulators, known as microRNAs (miRNAs), which have been shown to be important factors in the gene regulation of hypertension and possible therapeutic targets for this disease^[2]. The miRNAs are small, noncoding RNAs with approximately 17-25 nucleotides in length, which act as potent posttranscriptional regulators of gene expression. They can couple with sites in 3'-untranslated (3'-UTR) in the messenger RNAs (mRNAs) of protein-coding genes and negatively regulate their expression^[18-20]. The posttranscriptional regulation realized by the miRNAs in 3'-UTR is dependent on the degree of complementarity between them and the target mRNA. Thus, the miRNA does not require perfect complementarity for target recognition. Due to the fact that they have small sequences and act without the need for complete pairing^[21], a single miRNA can regulate up to 200 mRNAs, and more than one miRNA can regulate a single mRNA^[22].

As hypertension is developed on the basis of genetic susceptibility associated with environmental factors, many studies have shown associations between it and miRNAs; and others between it, miRNAs and ET as a way to prevent or minimize the harmful effects of environmental and/or genetic factors that promote hyperten-

sion. Based on the abovementioned data, the aim of this review is provide an overview of how ET can help to regulate blood pressure by means of specific miRNAs in the heart, vascular system, and skeletal muscle.

EFFECTS ON THE HEART

Hypertension is the major risk factor for congestive heart failure and chronically induces a chronic pressure overload on the heart. Sustained high blood pressure induces pathological cardiac hypertrophy (CH) and contractile dysfunction as compensatory mechanisms to reduce left ventricle wall stress. In addition to the increased size of cardiomyocytes, the growth of extracellular matrix is exacerbated and consequently there is interstitial fibrosis, and abnormalities occur in the systemic and coronary vasculature^[23].

Whereas, ET consists of a frequent, but intermittent stimulus of hemodynamic volume overload on the heart, which induces physiological CH. In this condition, the increase in size of the cardiomyocytes predominantly occurs by expression of sarcomere proteins, and the process is concatenated with preserved or improved cardiac function^[20]. Indeed, it is known that ET is able to decrease systolic and diastolic blood pressure in hypertensive humans and rats, and that the physiological CH or pathological CH triggers different signaling pathways, which in turn trigger specific transcription factors. Consequently, the pattern of gene expression is different in the two types of CH^[24-26]. In addition, there is an intricate network of transcriptional and posttranscriptional mechanisms involved in the differential expression of these genes, and there is still much to clarify as regards the differentiation of physiological and pathological phenotypes of CH^[26].

The miRNAs are part of the posttranscriptional mechanism, performing negative regulation of several target mRNAs involved in both physiological and pathological CH. The miRNAs are essential in different cell processes involved in the regulation of cardiovascular phenotypes, such as cardiomyocyte growth, remodeling, interstitial fibrosis, and heart failure. Several studies that postulate the relations between CH, hypertension and miRNAs have emerged. The miRNAs more frequently cited in cardiomyocytes studies are the miRNA-1, -133, -30, -21, -98, -378, -221, -22, -27, -212/132, -199 and -350 with several targets that are involved in the adaptive response of CH^[27,28].

Recent studies have supported the suggestion that CH may be caused by inflammatory signaling, and that this may be mediated by miRNAs. The miRNA-155 is expressed in macrophages and is a key mediator of cardiac injury in hypertensive heart disease, by the regulation of cardiac inflammation, dysfunction and hypertrophy in pressure overload^[29]. Moreover miRNA-155 directly targets endothelial nitric oxide synthase (eNOS) and the type 1 receptor of Angiotensin II (AT1R), primordial targets that regulate the tonus of vascular smooth muscle cells (VSMC), and hence the peripheral cause of pressure

overload on the heart^[29-32].

With regard to ET and CH, Fernandes *et al.*^[5] have shown that swimming training was able to increase miRNA-27a and 27b [targeting angiotensin-converting enzyme (ACE)] and to decrease miRNA-143 [(targeting angiotensin-converting enzyme 2 (ACE2)] in the heart of rats. The CH induced by ET involves the regulation of miRNAs related to increased AT1R expression without the participation of Angiotensin II. Parallel to this, the increase in ACE2, Angiotensin (1-7) and type 2 receptor of Angiotensin II in the heart has also suggested that miRNAs were involved in upregulation of the non-classic renin-angiotensin aldosterone system (RAAS), counteracting the classic cardiac RAAS in physiological CH^[5]. Thus, it is plausible to suggest a relationship between ET and CH through the regulation of several targets by miRNA-155, -27a, -27b, -143.

A hallmark related to hypertension and pathological CH is the reactivation of a set of fetal cardiac genes, which are repressed postnatally and replaced by the expression of adult genes. These genes include atrial natriuretic peptide/B-type natriuretic peptide, skeletal α -actin, and β -myosin heavy chain (β MHC). The causes and consequences of fetal gene expression in the adult heart have not been completely elucidated, but is known that chronic stress on the heart, such as hypertension, increases β MHC (slow ATPase activity) and decreases α MHC (fast ATPase activity), which has been implicated in impaired cardiac function^[13,33,34]. It is well known that in cardiovascular disease, the expression of β MHC increase while α MHC decreases and that ET is able to reverse these abnormalities in rats^[20,33,34].

The miRNAs -208a, -208b, and -499 are called “*myomiRNAs*”, which regulate the expression of slow myosin, playing an important role in the control of cardiac disease progression^[35-38]. The inhibition of miRNA-208a with Locked Nucleic Acid-Modified Anti-miRNA-208a (LNA-antimiRNA-208a) induced reversion in MHC switching during heart failure in hypertensive rats, reduced deleterious cardiac remodeling, and prevented the deterioration of cardiac function and lethality in rats^[39]. In another study, the circulating miRNA-16, -19b, -20b, -93, -106b, -223, and -423-5p were equally reversed by both LNA-antimiRNA-208a and captopril therapy, and the results were correlated with the changes in β MHC expression in the time course of hypertension or therapy in rats^[40]. With regard to ET, recent studies performed in our laboratory showed that ET decreases cardiac miRNA-208a expression in healthy Wistar and obese Zucker rats, induces upregulation of targets as THRAP-1, Pur β and Sox6, and improves the balance between the β MHC and α MHC gene expression^[41,42]. Thus, miRNA-208a is another pathological miRNA naturally reversed by ET, and its downregulation is involved in the increase in several targets that constitute a gene program to improve the contractile efficiency of the heart^[35]. Regarding circulating miRNAs, the miRNA-208a and -499 also reflect cardiovascular damage and a poor prognosis in patients with viral myocarditis, acute myocardial infarction, hyperten-

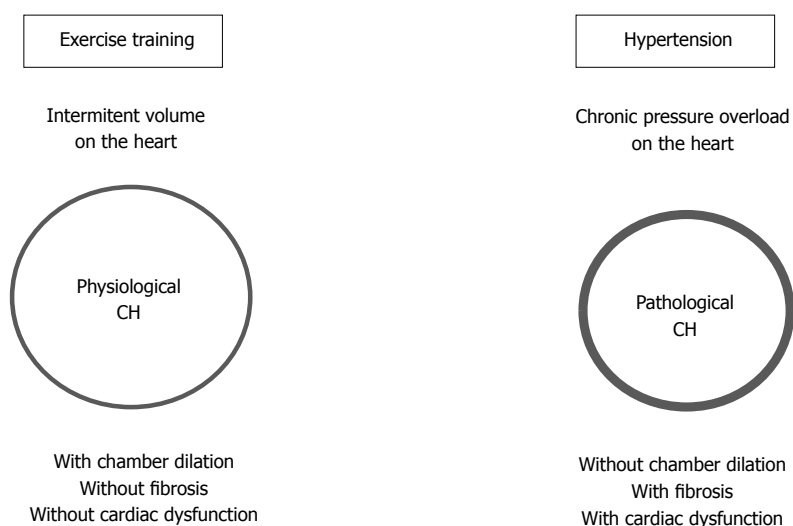


Figure 1 Effects of aerobic exercise training on the cardiac miRNAs in hypertension. CH: Cardiac hypertrophy; COL I : Collagen 1; COL III: Collagen 3; ACE: Angiotensin-converting enzyme; ACE2: Angiotensin-converting enzyme 2; THRAP-1: Thyroid hormone-associated protein 1; Purβ: Purine-rich element binding protein B; α-MHC: α-Myosin heavy chain; β-MHC: β-Myosin heavy chain.

Effect of exercise training	Targets	Phenotype	Effect of hypertension
↑ miRNA-29c	COL I ; COL III	Fibrosis	miRNA-29c ↓
↑ miRNA-27a ; miRNA-27b	ACE	Vascular resistance	miRNA-27a; ↓ miRNA-27b
↓ miRNA-143	ACE 2	Vasodilation	miRNA-143 ↑
↓ miRNA-208a	THRAP-1; Purβ; Sox6	Balance between α/β-MHC expression	miRNA-208a ↑

sion or diastolic dysfunction^[43].

Hypertension induces cardiac fibrosis. The aberrant expression of matrix extracellular proteins is determinant in the differentiation between pathological and physiological CH^[20,44]. There are also several miRNAs involved in the fibrotic response to stress and ischemic stimulus: the miRNA-21, -24 family, -29 family, -101, -206, -132, -214, involved in fibroblast survival, growth and differentiation or dysfunction of extracellular matrix^[44]. The downregulation of miRNA-29b induces upregulation of several extracellular matrix genes in the heart during pathological CH, including collagens and elastin^[45]. In addition, the miRNA-29c has recently been implicated in the immunopathogenesis of atrial fibrillation, showing a relationship between cardiac arrhythmia and abnormalities in miRNA-29c expression^[46]. ET is able to increase cardiac miRNA-29c expression, and a study conducted by Soci *et al.*^[20] has shown that swimming training increased miRNA-29c, and downregulated collagens I and III in the CH of rats. Thus, the future perspective related to fibrosis, immune system and cardiac automatism points to an integrative and regulatory role of miRNAs in the fibrotic response of the heart, requiring further investigations about miRNAs and its mRNA targets involved in the processes that regulate diastolic function, cardiac automatism and hypertension. Another interesting miRNA that plays an important role in the dysfunction of cardiovascular system is the miRNA-34a, which is induced in the ageing heart. The inhibition of this miRNA reduces fibrosis following the acute myocardial infarction and improves recovery of myocardial function^[47]. In this way, studies linking this miRNA, cardiac fibrosis, and ET will contribute to the knowledge and treatment of cardiovascular dysfunctions

in the future.

According to the studies conducted by our laboratory, ET is able to reverse or prevent pathological processes involved in hypertension^[5,20,24,25,48], but further studies are needed, and will be performed to investigate the relations between ET, hypertension, and CH in the perspective of miRNAs.

The Figure 1 summarizes the effects of ET or hypertension on some cardiac miRNAs.

EFFECTS ON THE VASCULAR SYSTEM

Macro- and microcirculation interact in the vascular system, and their changes contribute to end-organ damage in hypertension^[49]. However, these two vessel types must be discussed separately because they are differently regulated^[50].

Macrocirculation

Macrocirculation comprises large arteries such as the brachial, radial, femoral, aorta, epicardial arteries, and others vessels with the purpose of supplying blood from heart to peripheral tissues, and also performs the function of transforming the pulsatile flow into a steady flow necessary to supply oxygen to the tissues. In order to do this, good arterial compliance and distensibility are required, but in hypertension these properties of the arteries are affected^[51].

In hypertension, the structure, mechanical behavior and function of vessels are affected, with a reduction in lumen diameter and thickening of the tunica media (structural change), increased vascular stiffness (mechanical change), and impaired NO-dependent vasodilation

(functional change)^[51]. The direct relationship between hypertension and thickening of large vessels is due to an adaptive response of VSMC to increased internal arterial radius secondary to increased wall tensile stress imposed by pulsatile blood flow. Thus, VSMC become hypertrophied and change from the contractile phenotype to a proliferating phenotype. In addition, there is an increased collagen content in vessels, which contributes to increases in arterial thickness^[49]. Furthermore, hypertension promotes decreased endothelial NO production, which leads to more collagen expression and VSMC growth, affecting the vascular thickening and stiffness^[52]. In fact, NO is able to inhibit the expression of collagen, and lack of NO may induce excessive proliferation of VSMC^[53]. Thus, ET can act positively to prevent or reverse these vascular changes induced by hypertension, such as hypertrophic remodeling that may be caused by loss of mitogenic quiescence of VSMC, resulting in their proliferation and establishment of a hypertrophied phenotype^[53,54]. ET may also act on the vascular stiffness caused by high expression of collagen, which can be induced by hyperactivity of the renin-angiotensin system, and may also act on the impaired endothelium-dependent vasodilation, improving the NO availability^[51].

A large body of evidence has indicated that ET exerts positive effects on preventing or reversing the structural, mechanical, and functional vascular changes in hypertension. Indeed, Moraes-Teixeira *et al.*^[55] have shown that the effects of treadmill ET (1 h/d, 5 d/wk, 20 wk) were able to decrease the circumferential wall tension and intima-media thickness in the aorta of exercised spontaneous hypertensive rats (SHR) compared with non-exercised animals, without significant differences in the lumen diameter among the studied groups at the end of protocol. Moreover, treadmill exercise increased the percentage of elastic fibers; percentage of eNOS density in the aortic wall, and decreased blood pressure in exercised SHR compared with their non-exercised controls. These results were interesting, because they showed that ET was able to prevent or reverse the capacity of hypertension to modulate the thickening and stiffening of large vessels in rats. Furthermore, Guimarães *et al.*^[56] assessing arterial stiffness by carotid-femoral pulse wave velocity in hypertensive patients has shown that interval ET (16 wk of training) decreased arterial stiffness in trained subjects. In addition, aerobic ET (30 min, 3 times/wk, 4 wk) was able to reduced arterial stiffness in young men with a family history of hypertension^[57]. Jordão *et al.*^[58], have shown that treadmill exercise was able to reduce the mRNA expression of collagen I and III; prevent rupture of the internal elastic lamina, and improve the orientation of VSMC in the aorta of trained SHR compared with non-trained animals. Furthermore, endurance training attenuated the oxidative stress in the aorta of SHR, showing a possible suppressive effect of the exercise on the development of arteriosclerosis^[59], and was able to increase endothelium-dependent relaxation through NO pathways in the aorta of SHR^[60].

Microcirculation

Microcirculation is a network of vessels that includes the smallest arteries, arterioles, capillaries and venules which, by definition, have an inherent physiological characteristic of responding to increasing pressure by a myogenic reduction in lumen diameter, rather than a definition based on the vessel diameter and structure. Microcirculation has the function of optimizing nutrient and oxygen supply within the tissue in response to variations in demand; avoiding potential fluctuations in the pressure at the level of the capillaries, and determining the overall peripheral resistance^[49,61].

In hypertension, the mechanisms regulating vasomotor tone may be abnormal, leading to altered vascular function; and structural and mechanical alterations may also occur, such as an increased wall-to-lumen ratio and arterial stiffness. Furthermore, the rarefaction of arterioles and capillaries affecting the microvascular network has been observed in hypertension, and at first, it seems to be a functional change that involves the constriction of microvessels to the point of nonperfusion, and the second change is structural, when the nonperfused vessels may disappear. It is important to note that these factors will contribute differently in each vascular bed, and may vary between models of hypertension^[49,50,61]. Central to these alterations there is impaired NO availability, secondary to oxidative stress, mainly due to the increased production of reactive oxygen species and reduced antioxidant capacity, as well as increased cyclooxygenase-derived contractile products^[49,50,62-66].

Microvascular damage is a predictor of long-term adverse cardiovascular prognosis. Endothelial dysfunction has been considered an independent predictor of adverse cardiovascular events, providing a better predictive value of future cardiovascular events than each traditional risk factor alone identified in the Framingham study^[67]. Moreover, the abnormal artery structure and the arterial stiffness of small vessels are predictors of later cardiovascular events and have prognostic implications^[68-71]. As regards rarefaction, further prospective study is needed to determine whether it presents a clinically relevant predictive value, however it is important to note that microvascular rarefaction will reduce oxygen delivery resulting in ischemia, which may be responsible for much of the end-organ damage associated with hypertension^[49,61].

Given the central role that all these alterations play in vascular biology, it seems attractive to consider the relevance of therapeutic improvement in function, structure and mechanical alterations in hypertension. Thus, non-pharmacological approaches, such as ET, are able to improve blood pressure control and vascular alterations in hypertension. It is well established that ET decreases blood pressure^[24], and although endurance training, dynamic resistance training and combined training were associated with decreases in blood pressure, until clearer evidence emerges, it may be prudent to prescribe endurance training for the hypertensive individual^[24]. In accordance with Cornelissen *et al.*^[72], aerobic endurance training

decreases blood pressure through a reduction in vascular resistance.

Regular ET improves endothelial function in hypertensive patients as well as in animal models of hypertension^[73,74]. Although to a lesser extent, some recent studies have also confirmed the beneficial effects of continuous aerobic ET on the endothelial function of small arteries, such as in arteries of gastrocnemius muscle from rats with chronic NO synthase inhibition^[75]; in mesenteric resistance arteries and small coronary arteries from SHR^[15]; and in resistance arteries from young pre-hypertensive patients^[76]. Emerging evidence has increasingly demonstrated that diverse beneficial effects induced by ET in hypertension are mediated, at least in part, by reversing oxidant stress^[77]. In fact, in small arteries and arterioles the reduced oxidative stress significantly contributes to endothelium-dependent vasodilation that has been enhanced by ET^[15,78].

In addition to the functional improvement, structural and mechanical changes are also mediated by exercise in hypertension. Recently, we demonstrated that aerobic treadmill exercise reverts the increased arterial stiffness of both mesenteric resistance and small coronary arteries, mediated by changes in the extracellular matrix^[15], although it did not modify the increased wall-to-lumen ratio of these arteries in hypertension. However, the vascular remodeling induced by ET may be dependent on the vascular bed studied, and thus either improvement^[79,80] or no effects^[15,79,80] already have been observed in microcirculation in hypertension. In addition to structural changes, aerobic ET corrects capillary rarefaction in hypertension^[7,79]. Indeed, a balance between angiogenic and apoptotic factors to prevent microvascular abnormalities in hypertension has been observed as an effect of ET^[7]. In addition, the decrease in oxidative stress induced by ET in SHR seems to be associated with the normalization of the reduced number of endothelial progenitor cells in a vascular endothelial growth factor (VEGF)/eNOS-dependent pathway, thus promoting a peripheral revascularization induced by aerobic ET^[11].

Although many vascular effects of ET have been established in hypertension, little is known in the literature about their beneficial effects on miRNAs of the small and large vessels. However, recently new approaches in ET have highlighted the key role of miRNAs in the modulation of hypertension.

The miRNAs are involved in all biological processes, including cellular proliferation, differentiation, cellular migration and apoptosis, and their deregulation often results in the development of cardiovascular diseases. As there is high expression of miRNAs in the vascular system, growing evidence suggests that miRNAs may be important in the development of endothelial dysfunction, vascular remodeling and reduced angiogenic capacity, features that are frequently observed in the pathogenesis of hypertension^[2,81,82]. More specifically, the phenotypes of VSMC and endothelial cells, as well as the inflammatory activation of macrophages is regulated by miRNAs, which may promote the structural changes that lead to

vascular remodeling^[83]. VSMC maintains remarkable plasticity, able to react to various forms of vascular stress or injury by switching from the contractile phenotype to a proliferating and synthetic phenotype^[2].

Studies have associated hypertension and alterations in the expression of miRNAs with the angiogenic process, endothelial dysfunction, changes in the RAAS, and in the phenotype of VSMC^[2], but as regards the role of ET, there is almost nothing in the literature showing a direct connection between the modulation of miRNAs and vascular changes in hypertension. For example, nothing has yet been shown in the literature relating hypertension and the effects of exercise to the miRNAs existing in aorta. However, considering the atherosclerosis, Wu *et al*^[84] investigated the effects of treadmill ET for a period of 12 wk, 5 times per week, 60 min/d, on the aorta of male ApoE null C57BL/6J mice with atherosclerosis, which were fed a high-fat diet. The authors showed that ET significantly decreased the angiotensin II and endothelin 1, and prevented the formation of plaques and foam cells in comparison with the control group, followed by decreased expression of miRNA-155, and increased expression of miRNA-146a and miRNA-126 in the aorta of the trained mice, with more pronounced changes in the groups treated with Simvastatin. The miRNA-146a interacts with the 3'-UTR of the tumor receptor-associated factor 6 (TRAF6) gene, negatively impacting the toll-like receptor 4 (TLR4)-TRAF6 signaling, and then reduces the inflammatory response in atherosclerosis^[85]. The decrease in miRNA-155 expression is an essential factor for increasing eNOS expression and NO production, because eNOS is directly targeted by this miRNA^[31,86]. In atherosclerosis, miRNA-155 is drastically upregulated^[31], because inflammation factors increase miRNA-155 *via* activation of nuclear factor (NF)- κ B, activator protein-1, and Rho kinase. The miRNA-155, together with yet unidentified cytosolic RNA-binding proteins, bind to the eNOS mRNA 3'-UTR and destabilize eNOS mRNA, resulting in decreased eNOS and NO production. However, anti-miRNA-155, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) and other Rho kinase inhibitors prevent the increase in miRNA-155^[86], and then maintain the eNOS and NO production, or possibly increase their production. However, in hypertension, could ET diminish miRNA-155 expression in vessels? To our knowledge, at present there are no studies to answer this question. Nevertheless it is known that exercise can modulate the miRNA-155 expression in atherosclerotic vessels.

The study of Wu *et al*^[84] has also shown that ET was able to increase the miRNA-126 expression in the aorta of the studied mice. The miRNA-126 suppresses the cell adhesion molecule expression and negatively regulates the endothelial receptor of α 4 β 1 integrin, thereby interfering with adhesion of leucocytes to the endothelium^[87,88], as well as enhancing angiogenesis^[87]. In agreement with Harris *et al*^[87], miRNA-126 is expressed in endothelial cells, but not in VSMC, and miRNA-126 in other tissues might simply reflect the vascularity of the organ. Target deletion of miRNA-126 in mice promotes hemorrhaging, loss of

Table 1 Vascular effects of hypertension and exercise training in macro- and microcirculation

Hypertension	Exercise training	Ref.
Hypertrophy of VSMC	Decreased intima-media thickness	[49,52,55-57]
Excessive proliferation of VSMC	Improved orientation of VSMC	[49,53]
Increased collagen content	Decreased mRNA collagen expression	[49,51,58]
Decreased availability endothelial NO	Increased endothelial NO production	[49,51,55]
Increased endothelium-dependent contract factors	Increased endothelium-dependent relaxation	[59,75]
Increased ROS production	Increased antioxidant capacity	[49,50,59,62-66]
Increased overall peripheral resistance	Reduced vascular resistance	[24, 49,50]
Rarefaction of arterioles and capillaries	Increased peripheral revascularization	[7,49,50,61,79]

VSMC: Vascular smooth muscle cells; NO: Nitric oxide; ROS: Reactive oxygen species.

Table 2 Some miRNAs associated with hypertension that has potential to be regulated by exercise training

miRNAs	Targets	miRNA function	Ref.
miRNA-16	VEGF	Control of angiogenesis and vascular integrity	[7]
miRNA-21	PTEN; Bcl-2	Involved in nitric oxide production; apoptosis	[2,7,80,82]
miRNA-24	Trb-3	Mediator of contractile phenotype in VSMC	[81-83]
miRNA-92a	Integrin $\alpha 5$; eNOS	Involved in the regulation of endothelial function	[88]
miRNA-126	VCAM-1; PI3KR2; Spred1	Suppress cell adhesion molecule; Proangiogenic	[48,85,87,88]
miRNA-143/145	KLF4; KLF5	Involved in the plasticity of VSMC	[81]
miRNA-146a	TRAF6; KLF4	Involved in inflammatory response	[85]
miRNA-155	eNOS; AT1R	eNOS expression and NO production	[85]
miRNA-221/222	P27Kip1	Involved in the proliferation of VSMC	[81]

VEGF: Vascular endothelial growth factor; PTEN: Phosphatase and tensin homolog; Bcl-2: B-cell CLL/lymphoma 2; Trb-3: Tribbles-like protein-3; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; VCAM1: Vascular cell adhesion molecule 1; PI3KR2: Phosphatidylinositol 3-kinase regulatory sub-unit beta; Spred1: Sprouty-related; EVH1: Domain-containing protein-1; KLF4: Krüppel-like factor 4; KLF5: Krüppel-like factor 5; TRAF6: TNF receptor-associated factor 6; AT1R: Type 1 receptor of angiotensin II; P27Kip1: Cyclin-dependent kinase inhibitor 1B.

vascular integrity and defects in endothelial cell proliferation, migration and angiogenesis^[89]. The miRNA-126 is one of the most abundant miRNA in endothelial cells, and plays an anti-atherogenic role by enhancing endothelial repair^[2,82,84].

Another miRNA that deserves to be remembered is the miRNA-34a because its overexpression has been associated with senescence of endothelial cells. This miRNA targets SIRT1 (sirtuin 1) in the endothelial cells^[90] and may serve to mediate the effect of aging upon the vasculature^[91]. The inhibition of SIRT1 impairs the eNOS metabolism in the endothelial cells *via* SIRT1/eNOS axis^[92,93], allowing us to suppose that this miRNA may be related with development or progression of atherosclerosis or hypertension. However, such as in heart, the literature has not shown studies linking the miRNA-34a, vascular cells, and ET.

In addition to the above mentioned data, other miRNAs are able to participate in the vascular changes. In this case, the miRNA-143/145 cluster is related to the phenotype plasticity of VSMC, and together with miRNA-21 and miRNA-24, they are involved in the differentiation and proliferation of these cells. Thus, several studies have shown that they are downregulated in injured vessels^[2,81-83]. The miRNA-21 is involved in vascular remodeling that affects both VSMC and endothelial cells. The overexpression of miRNA-21 induces a synthetic VSMC phenotype, as observed after vascular injury, and it is also a critical miRNA for angiogenesis^[2,81,82]. The miR-

NA-221/222 have an ambiguous response after vascular injury, enhancing the proliferation of VSMC, whereas it may be atheroprotective in endothelial cells^[81,83]. The miRNA-221/222 may also be involved in the control of eNOS expression^[94]. The miRNA-92a is a negative regulator of endothelial function, and its overexpression represses *eNOS* gene expression and angiogenesis^[88]. The abovementioned miRNAs have been found to be related to hypertension. B tkai *et al*^[2] and Synetos *et al*^[95] provided an overview of the role of miRNAs in the development and consequences of hypertension.

Recent data from our research group has shown the effects of ET on vascular miRNAs involved in hypertension. Our study reveals some of the molecular mechanisms of ET in physiological revascularization observed in hypertensive rats. Swimming ET restored the balance between injury and repair in the vascular process collaborating with the regression of hypertension, and remarkably, restoring normal expression of skeletal muscle microcirculation miRNA-16, -21, and -126^[7]. This alteration occurred parallel with normalization of VEGF, eNOS, and PI3KR2 levels, as well as the proapoptotic (Bad) and antiapoptotic (Bcl-2, Bcl-x, and p-Bad_{ser112}:Bad ratio) mediators, indicating that balance between angiogenic and apoptotic factors may prevent microvascular abnormalities in hypertensive rats^[7].

The study of miRNAs may generate hypotheses about the mechanisms by which exercise affects the pathophysiology of hypertension. ET probably causes al-

terations in many of the miRNAs that are deregulated in the vascular system. Thus, a promising tool emerges for the treatment and expansion of knowledge about hypertension.

Effects of hypertension and ET in the vascular system are summarized in Table 1, and some miRNAs, its target, and miRNA function are in the Table 2.

EFFECT ON THE SKELETAL MUSCLE

Microvascular abnormalities, such as reduction in blood flow and microvascular rarefaction, are clear evidence of disturbance of the angiogenic process related to changes in the muscle fiber profile in hypertension^[61,96,97].

It is interesting to note that studies have shown that ET-induced blood pressure reduction in SHR was correlated with both normalization of arterial wall-to-lumen ratio and a great increase in capillary-to-fiber ratio in skeletal muscle. Indeed, evidences have shown that ET improves both endothelial function and muscle fiber profile, counteracts microvascular rarefaction and decreases blood pressure in hypertension^[7,11,79,80,98].

It is known that the angiogenesis represents a primary adaptive response of the skeletal muscle to aerobic ET, hence contributing to the improvement in muscular aerobic capacity (oxygen transportation, provision and extraction)^[79]. On the other hand, many conditions, such as cardiovascular disease (CVD) risk factors, lead to alteration in the capillary support of skeletal muscles, and may consequently, impair the offer of oxygen and nutrients, which is related to alteration in the distribution of the skeletal muscle fiber types towards an increase in type II fibers. As yet, little is known about the origin of the transition from type I fibers to type II in the soleus muscle of SHR; however, studies have shown that it is related to capillary rarefaction followed by alterations in metabolic properties^[96,99].

Studies have shown that when there is a transition between the types of fibers of the skeletal muscle, the different morphological properties of the muscular fiber are changed in the following manner: the capillary density and activities of the energy metabolism enzymes are altered at an early stage during the transition, and precede the change in myofibrillar ATPase activity and the contractile characteristics of the muscle^[100].

In mammals, the skeletal muscle fibers are usually classified as type I and type II fiber, according to the different activities of the myosin ATPase after pre-incubation at different pHs, and the type II fibers can be sub-classified into II A, II X/D and II B. The type II fibers are characterized as being fast twitch with predominance of glycolytic metabolism, while the type I fibers are slow twitch with predominance of oxidative metabolism^[96].

Evidences in the literature have shown that the skeletal muscle of hypertensive individuals, and of SHR, contains a higher percentage of type II fast twitch, glycolytic fibers compared with their normotensive controls^[7,96,100,101]. It is interesting that the results obtained in the analysis of the composition of the fiber types of the

soleus skeletal muscle (which presents an average of 90% of type I fibers and 10% of type II fibers), performed both by histochemical myosin ATPase reaction and SDS-PAGE gel electrophoresis for detection of MHC for each type of fiber, were positively correlated regardless of the technique applied^[101]. According to Bortolotto *et al.*^[101] the main result obtained in their study was that in all stages of hypertension (4, 16 and 24 wk), the soleus muscle of SHR presented a higher proportion of type II fibers than the soleus muscle of Wistar Kyoto rats (WKY), as well as hybrid fibers, those that contain two types of MHC in the same muscle fiber isolate, in the case of SHR, a higher proportion of II A + II X hybrid fibers. The presence of a higher proportion of hybrid fibers is an indication of the transition of muscle fiber type in the muscle under consideration.

Some studies have associated the effects of ET with pharmacological treatment. Minami *et al.*^[102] showed the effects of ET either associated with treatment with perindopril (ACE inhibitor) or without it, on the capillarity and fiber types in the soleus muscle of SHR. The authors observed that chronic treatment with perindopril increased the exercise capacity in untrained animals; however, this effect was not synergic to the exercise capacity acquired as a result of ET alone. Whereas, the treatment with perindopril associated with ET promoted adaptive alterations in the soleus muscle, such as increase in capillary density and percentage of type I fibers^[102]. Although no alteration in the composition of types of fiber was observed in the trained SHR and SHR treated with perindopril groups when compared with the sedentary SHR group, the authors observed higher capillarization in these groups, which may be attributed to the improvement in exercise capacity. A more recently study from the same group showed that pharmacological treatment with a calcium channel blocker (azelnidipine), or a type I angiotensin I receptor antagonist (olmesartan) or even the ET significantly increased capillary density and percentage of type I fibers in the soleus muscle of SHR^[103]. Although the results in the literature are still controversial with respect to the alterations in proportion of the types of fiber in response to ET, it was also not possible to observe the comparison between the profile of the types of fiber in the trained SHR group compared with its normotensive control WKY, with the aim of checking normalization with the fiber type composition.

Recently, Fernandes *et al.*^[7] for the first time, showed evidence that aerobic ET corrected the alteration in the composition of fiber types in the soleus muscle of SHR when compared with WKY. This result is probably linked to the increased capillarization and citrate synthase activity observed with ET, since these adaptations are related to changes in fiber type in the skeletal muscle. Altogether, these ET-induced adaptations contribute to the increase in oxygen consumption and exercise tolerance, and the decrease in BP levels observed in the trained hypertensive group.

Although studies have reported change in the profile of skeletal muscle fibers in hypertension, none of them

observed change in muscle mass in hypertensive rats up to 24 wk of age^[7,96,100,101,104]. It is interesting that Carvalho *et al.*^[105] determined the soleus muscle changes in the expression of MHC isoforms, diameter of fiber types and muscle atrophy during the transition of ventricular hypertrophy to heart failure induced by aortic stenosis. The animals developed a myopathy in the soleus muscle, characterized by a decrease in the percentage of type I fibers and increased frequency of type IIa fibers, in cardiac hypertrophy (after 18 wk) and heart failure (after 28 wk). However, atrophy of type IIa fibers occurred only during heart failure.

Recently, for the first time in the literature, Damatto *et al.*^[106] reported changes in MHC isoforms and soleus muscle atrophy induced by heart failure in SHR. The setting of heart failure in SHR at 18 mo of age was observed and muscle disorders were associated with myogenic regulatory factors and expression of myostatin and follistatin.

Many studies have shown the beneficial effect of ET on muscle atrophy and correction of changes in fiber types in animals with heart failure due to various etiologies, such as myocardial infarction, and sympathetic hyperactivity^[99,107], however no study up to now has reported the effects of ET on these changes in animals with heart failure with the etiology of hypertension.

In spite of the important role of exercise in the prevention and treatment of hypertension, the mechanisms involved in these vascular and muscle changes are not fully understood. The analysis of miRNAs has made it possible to understand the development of various types of CVD, and the elucidation of these processes regulated by miRNAs and identification of new targets of miRNA in the pathogenesis of disease is a very valuable strategy for both prevention and treatment of hypertension.

Recent studies have revealed that myogenic transcription factors involved in differentiation and muscle contraction also activate the expression of a set of miRNAs with the function of “adjusting” the output of the transcription network, resulting in precise cellular responses to signals of development, physiology and pathology. The integration of these small RNAs into the muscle transcriptional program further expands the accuracy and complexity of the regulation of genes in muscle cells, since miRNAs are capable of regulating various mRNAs, and mRNAs can be targets of many miRNAs^[108-110].

The miRNAs-1, -133a-b, -206 and -208 are muscle-specific and have been studied thereby contributing to muscle development. It is interesting that these miRNAs provide up to 25% of miRNAs expressed in skeletal muscle; they are recognized by their control of the growth, differentiation and contractility of muscle^[111-116]. Additional miRNAs have been described; these regulate myoblast proliferation or differentiation, and include miRNAs-24, -26a, -27b, -125b, -148a, -181, -214 and -489^[116-119]. Curiously, high expression of miRNA-128a was found in skeletal muscle, and increased during myoblast differentiation, regulating target genes involved in insulin signaling, which include insulin receptor (Insr),

insulin receptor substrate 1 (Irs1) and phosphatidylinositol 3-kinases regulatory 1 (Pik3r1). In fact, Motohashi *et al.*^[116] showed that overexpression of miRNA-128a in myoblasts inhibited cell proliferation by targeting Irs1. In contrast, inhibition of miRNA-128a induced myotube maturation and myofiber hypertrophy *in vitro* and *in vivo*.

The miRNAs-1 and -133 are expressed in cardiac and skeletal muscle and they are transcriptionally regulated by myogenic differentiation factors, such as MyoD, myogenin, Mef2 and SRF (serum response factor)^[110-113]. The miRNA-1 promotes differentiation of cardiac and skeletal progenitor cells and exit from the cell cycle in mammals^[109], while the miRNA-133 inhibits differentiation, and maintains cells in a proliferative state^[111].

Increased expression of miRNA-1 in skeletal muscle of mice after 3 h of a single session of aerobic ET was observed by Safdar *et al.*^[120]. This increase was associated with a reduction in the expression of its target histone deacetylase 4 (HDAC4), a transcriptional repressor of muscle gene expression, and by the increase in myogenic differentiation factors such as MyoD, and thus would promote remodeling of the lesion caused by the training session^[113,120]. Conversely, the chronic effect of exercise led to a decrease in the expression of miRNA-1 associated with muscle hypertrophy in favor of the expression of important genes in muscle growth, such as c-Met, hepatocyte growth factor and Insulin-like growth factor 1 (IGF-1). IGF-1 is a potential target of miRNA-1, which could partly explain the hypertrophic phenotype during the initial responses resulting from ET overload^[121,122].

The miRNA-206 is the only miRNA specifically expressed in skeletal muscle, and its expression appears to be induced by MyoD and myogenin during myogenesis, promoting differentiation^[113,114,123]. HDAC4, PAX7, MET and Notch3 are some of the target *miRNA-206* genes related to the muscle differentiation process^[113,115,123].

These skeletal muscle miRNAs also appear to participate in muscle diseases including cardiac hypertrophy, heart failure and muscular dystrophy, such as Duchenne muscular dystrophy^[113,115,122,124].

Studies have reported that an intron of the α MHC (*Myh6*) gene encodes a miRNA -miRNA-208a, which is necessary to increase β MHC (*Myh7*) in the heart of adult animals in response to stress and hypothyroidism^[35]. Given that miRNA-208a and their host myosin, α MHC, are only expressed in the heart, these results raise interesting questions with respect to which other miRNAs could control the fiber type and gene program in skeletal muscle contractile proteins^[38].

van Rooij *et al.*^[38] showed the existence of two miRNAs in MHC genes. The β MHC gene encoding the miRNA-208b, which has an identical sequence to the seed miRNA-208a, and differs at only three nucleotides in the 3' region. A third member of this family is miRNA-499, encoded by the gene *Myh7b*, a little studied myosin that shares extensive homology with the β MHC gene. These two miRNAs are expressed in skeletal muscle, are related with an oxidative profile, such as in the soleus, and have a feature of type I fibers with predominance of β MHC.

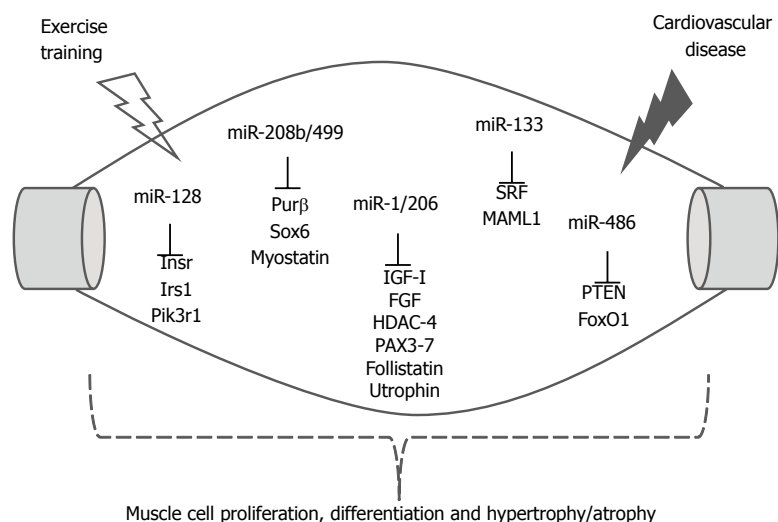


Figure 2 Skeletal muscle miRNAs and selected target genes regulating cell proliferation, differentiation and hypertrophy/atrophy by exercise training and cardiovascular diseases. The relationship between miRNAs and the mRNAs that encode proteins is shown. Insr: Insulin receptor; Irs1: Insulin receptor substrate 1; Pik3r1: Phosphatidylinositol 3-kinases regulatory 1; Purβ: Purine-rich element binding protein B; HDAC4: Histone deacetylase 4; IGF-1: Insulin-like growth factor 1; FGF: Fibroblast growth factor; SRF: Serum response factor; MAML1: Mastermind 1; PTEN: Phosphatase and tensin homolog; FoxO1: Forkhead box protein O1.

Interestingly, deletion of miRNA-208b and miRNA-499 did not alter the expression of another miRNA in the soleus muscle, and the analysis of fiber type showed little or no difference in the number of type I muscle fibers in any of the mutant animals compared with the wild type. However, in the generation of double knockout animals (dKO) for miRNAs-208b and -499 there was a substantial loss of type I muscle fibers in the soleus muscle of dKO. The loss of slow fibers in dKO mice was also evident from the reduction in protein and gene expression of β MHC, and a concomitant increase in the expression of isoforms of myosin fast type IIa and type II b and II x^[38].

Moreover, overexpression of miRNA-499 was sufficient to induce complete conversion of all fibers from soleus fast into slow fibers with a type I profile. Notably, when the animals were subjected to an exercise tolerance test on the treadmill, those with overexpression of miRNA-499 ran 50% more than the wild-type, indicating a higher aerobic endurance resulting from the reprogramming of muscle fibers with the induction of predominance of type I fibers, slow-twitch and oxidative metabolism. Moreover, the authors investigated the possible targets of these miRNAs related to the control of β MHC. The findings showed that the transcription factors Sox6 (a member of family Sox transcription factors) and Purβ are targets of miRNA-208b and -499 in skeletal muscle, and dKO animals have increased expression of both factors^[38]. Other studies have also shown that Sox6 and Purβ inhibit the expression of β MHC in skeletal muscle involved in changing the profile of muscle fibers^[125,126].

No studies have been conducted to evaluate the expression of these miRNAs and change in fiber type in CVD, in particular in hypertension. Knowing that in hypertension and CVD there is a change in muscle fiber profile, it would be appropriate to think that miRNAs-208b and -499 would participate in this change and that aerobic ET would be a strong candidate for the standardization of these parameters, since it is well known that ET increases the oxidative metabolism associated with a

predominance of type I fibers (Figure 2).

CONCLUSION

Considering that hypertension affects over one billion people across the world, that ET plays a key role as non-pharmacological therapy for hypertensive patients, and that genic therapies from miRNAs may represent new strategies in combating the development and/or progression of hypertension, is reasonable to go more deeply into studies to acquire more knowledge about which miRNAs are induced by ET and which are related to protection of the cardiovascular system. Most important, these studies may guide scientists in future gene therapies for the treatment of hypertension with specific miRNAs. Finally, complementing the above discussion is important to comment about circulating miRNAs that results of cellular damage and that have been presented as biomarkers of cardiovascular diseases^[127]. In this way, the circulating miRNA-1, -133a, and -208b were higher in patients with myocardial infarction in relation to patients who had unstable angina^[128], and the miRNA-499 was increased in individuals with acute myocardial infarction compared with patients without myocardial infarction^[129]. Also, patients with coronary artery disease or diabetes may presents reduced levels of circulating endothelial-enriched miRNAs, such as miRNA-126^[130]. Moreover, it was reported a linkage between circulating miRNAs, human cytomegalovirus, and essential hypertension^[131]. On the other hand, the literature has not presented studies linking circulating miRNAs, cardiovascular diseases, and ET. In this way, further studies need be realized. However, it is clear that circulating miRNAs will be used in the future also as biomarkers of the therapeutic efficacy of ET in the treatment of hypertension.

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P- Reviewer: Beltowski J, Durandy Y, Okumura K, Waisberg J, Wang M **S- Editor:** Ji FF **L- Editor:** A **E- Editor:** Wu HL





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