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Junjie Xiao *Editor*

Exercise for Cardiovascular Disease Prevention and Treatment

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Exercise for Cardiovascular Disease Prevention and Treatment

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Part I
Exercise Benefits the Heart: Clinical Evidence

Chapter 1
Exercise Benefits Coronary Heart Disease

Lei Wang, Dongmei Ai, and Ning Zhang

Abstract Coronary heart disease (CHD) is a group of diseases that include: no symptoms, angina, myocardial infarction, ischemia cardiomyopathy and sudden cardiac death. And it results from multiple risks factors consisting of invariable factors (e.g. age, gender, etc.) and variable factors (e.g. dyslipidemia, hypertension, diabetes, smoking, etc.). Meanwhile, CHD could cause impact not only localized in the heart, but also on pulmonary function, whole-body skeletal muscle function, activity ability, psychological status, etc. Nowadays, CHD has been the leading cause of death in the world. However, many clinical researches showed that exercise training plays an important role in cardiac rehabilitation and can bring a lot of benefits for CHD patients.

Keywords Coronary heart disease • Exercise • Rehabilitation

1 Side-Effect of Lacking Exercise

Even for normal people, lacking of exercise can cause many negative consequences. With the atrophy of muscle fibers, the reduction of muscle power and the muscle mass, the oxidation capacity of muscle decrease at the same time. Research showed that with the increase of age every year, oxygen consumption decrease by 0.1MET, indicating that physical fitness level decreases when age increases [1]. Another study showed that oxygen uptake will have a reduction of 0.2 MET for 1-day bed rest, indicating that bed

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rest has a negative effect on cardiovascular function [2]. So, what about CHD patients? Lacking exercise can cause tachycardia, orthostatic hypotension and increased risks of thromboembolism. Elderly patients would have a reduction in muscle groups and physical function. If VO_{2max} (maximum oxygen uptake) is too low to complete daily activities (the impaired ability to cross street safely, go up the stairs, stand up from chairs or toilet), the quality of life will have a dramatic decline for the elderly.

2 Beneficial Effects of Exercise on Coronary Heart Disease

2.1 Aerobic Exercise

Aerobic exercise, the most studied and recommended modality, with a beneficial dose-response effect on prognosis [3, 4, 5], consists of movements of large muscle mass in rhythmic manner for a sustained period. The aerobic exercise includes everyday activity, for instance, active travel (cycling or walking), heavy household work, gardening, occupational activity, leisure time activity, or exercise such as brisk walking, Nordic walking, hiking, jogging or running, cycling, cross-country skiing, aerobic dancing, skating, rowing or swimming. Similar to all other interventions, its prescription can be adjusted in terms of frequency, duration and intensity [6]. However, to achieve the most optimized beneficial effect, patients with CHD should get individualized prescription. So, what beneficial effects can aerobic exercise bring for CHD?

2.1.1 Improved Heart Functions

Aerobic exercise training could increase the diameter and the elasticity of coronary arteries, improve endothelium function to optimize the structure and function of coronary arteries, facilitate the establishment of coronary collateral circulation, compensate adaption of improved blood supply for coronary arteries and stabilize coronary arteries clots. In addition, it can increase blood flow and reduce new pathological changes. Study showed that long-term regular aerobic exercise can improve physical function and decrease heart rate, SBP (systolic blood pressure), RPP (heart rate-blood pressure product), myocardial oxygen consumption, and increase the threshold of exercise-induced myocardial ischemia during submaximal exercise [7]. Moreover, aerobic exercise training after MI (myocardial infarction) has also been suggested to improve ventricular function and attenuate ventricular remodeling. Patients with an initial Q-wave MI and a left ventricular ejection fraction <10% in the ELVD (Exercise and Left Ventricular Dysfunction) trial received 6 months of exercise training. There was a resultant increase in both exercise capacity and left ventricular ejection fraction (34–38%) [8].

2.1.2 Increase Exercise Capacity

Aerobic exercise is critical to increase cardiopulmonary exercise tolerance and improve cardiovascular function for CHD patients. Research showed that VO_2 peak of patients with heart diseases has an increase of 11–36% after exercise training for 3–6 months, and the poorer the patient's condition is, more improvement he or she will achieve [9]. With improved exercise tolerance, the quality of life will be better at the same time so that the elderly can have the ability to complete daily life activities independently, which is of vital importance for the improvement of the elderly's psychology, and the release of the pressure on family and the whole society [10]. Meanwhile, the improvement of exercise tolerance is closely associated with prognosis, independent from other cardiovascular risk factors [11]. One study showed that the survival rate of patients with exercise tolerance less than 10 MET is obviously lower than the one with exercise tolerance more than 18 MET. Another study had a similar conclusion, the survival rate of cardiovascular patients with exercise tolerance less than 5 MET is significantly lower than the one with exercise tolerance more than 8 MET [12].

2.1.3 Reduce Risk Factors of CHD

Common risks factor of CHD are smoking, hypertension, abnormal lipid levels, obesity and diabetes [13]. Many researches demonstrated that aerobic exercise and regular physical activity can moderately reduce body mass and body fat content [14, 15], hypertension [16], blood triglyceride, and increase HDL (high density lipoprotein cholesterol) [7, 17], optimize insulin sensitivity and glucose metabolism [18] to decrease the risk of type 2 diabetes for patients with abnormal glucose tolerance [19].

2.1.4 Reduce the Incidence Rate, Complication, Recurrence Rate, Mortality of CHD

Lacking of enough attention to the rehabilitation after CHD would make patients miss the appropriate medical guidance in time, leading to the recurrent morbidity and hospitalization. This could cause immense burden of health care cost for individuals and for the whole society as well. Fortunately, the benefits of exercise training in CHD have got strong evidence. Lots of clinical researches showed that proper cardiac rehabilitation with exercise training can effectively and efficiently reduce the all-cause mortality by 8–37% and cardiovascular mortality in patients after MI [20, 21]. Additionally, numerous researches demonstrated that cardiac rehabilitation program with exercise training can delay the whole development progress of atherosclerosis and thus reduce the morbidity and hospitalization rate of acute ischemia coronary arteries events, and the risk rate of sudden death for patients with acute myocardial infarction (AMI) (the risk of sudden death of patients who accepted cardiac rehab was decreased by 45%) [22, 23]). Exercise also appears

beneficial for patients with stable CHD. A small number of men with angina and angiographic evidence of CHD showed significantly more 1-year survival free of cardiac events following exercise training than those with PCI (percutaneous coronary intervention) with stenting: 88% vs. 70%.

2.2 Resistance Exercise

Resistance exercise targets the major muscle groups and includes multi-joints or compound movements through the full range of motion of the joints, such as walking with resistance bands, calisthenics using body weight for resistance, carrying heavy loads and heavy gardening. The resistance exercise used for CHD is cyclic: a series of moderate load, continuous, slow, big muscle group and repetitive. Common methods are using own body mass (such as push-ups), dumbbell or barbell, sports equipment and thera-band exercise.

Compared to aerobic exercise, resistance exercise can induce lower heart rate reaction, and mainly increase the pressure load of heart to enhance blood perfusion in order to achieve a better oxygen supply and demand balance of myocardium. Other benefits include: increasing skeletal muscle mass, increasing basic metabolic rate; preserving and enhancing muscle mass, strength, power, endurance to improve exercise tolerance and functional ability to help patients return to normal life and social work. Researches demonstrated isotonic exercise training benefits in lipid and BP (blood pressure) control and insulin sensitivity, especially in combination with aerobic exercise which is of great significance for reducing the risks of CHD [24].

2.3 Flexibility Exercise

To realize the optimal benefits of exercise training, patients should have good function status of skeletal muscles, which requires patient's range of motion (ROM) in a desirable range. It is imperative to keep the elasticity and flexibility of upper and lower trunk, cervical region and buttock. Also, if these parts of body lacked flexibility, it would increase the risk of chronic cervical, shoulder, back and lumber pain. The elderly usually get poor flexibility which could reduce their capacity for daily living activities and exercises.

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Chapter 2
Exercise Exerts Its Beneficial Effects on Acute Coronary Syndrome: Clinical Evidence

Zhuyuan Liu, Huanyu Gu, Qiying Dai, Hongbao Wang, Jianhua Yao, and Lei Zhou

Abstract Acute coronary syndrome (ACS) is characterized with high morbidity, high mortality, long hospitalization and frequent revisits. It has been the most serious coronary artery diseases in the world. A large body of clinical evidence demonstrates that exercise is associated with reduced cardiovascular disease risk. In addition, different types of exercise have become the central to most cardiac rehabilitation/risk reduction programs. However, the detailed effects of exercise in ACS is still unclear and there is still lack of evidence on which exercise regimen may be ideal for ACS. This chapter presents a brief review of the pathophysiology of ACS and the relationship between exercise and the cardiovascular system. Besides that, this chapter also provide an updated discussion of the most relevant discoveries regarding to exercise and its role in managing ACS in clinical studies.

Keywords Acute coronary syndrome • Exercise • Cardiovascular disease • Clinical evidence

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Zhuyuan Liu, Huanyu Gu and Qiying Dai contributed equally to this work.

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1 Introduction

Coronary artery disease remains the first cause of mortality worldwide [1]. Coronary artery disease contributes to the major cause of cardiovascular mortality, being responsible for approximately seven million of deaths [2]. Among all types of coronary artery diseases, acute coronary syndrome (ACS) is the most serious one. Each year in America, there are approximately 635,000 new diagnosed ACS patients [3–8]. It is also associated with longer hospitalization and more frequent revisits [9, 10].

Although the mortality of ACS has declined substantially [11], the situation stays critical. It is estimated that 40% of patients who experience a coronary event will have increased risk of death within 5 years but the risk can be 5–6 times higher in individuals who experience a recurrent event [12–14]. The economic burden due to ACS is also quite huge. The cost of one patient in 1 year is estimated to be from US$22528 to US$32345. The majority of the cost is due to hospitalizations [15, 16]. Given its deleterious impact on health economic consequences, it has been required to have evidence-based management for these patients.

ACS refers to the dysfunction of cardiac muscle due to decreased blood flow in the coronary arteries [17]. ACS is usually divided into three categories: ST elevation myocardial infarction (STEMI, 30%), non ST elevation myocardial infarction (NSTEMI, 25%), or unstable angina (38%) [18]. Physical well-being may improve cardiac-related outcomes [19]. Back into the early 1950s, standard treatment of myocardial infarction (MI) was several weeks of hospitalization followed by months of restriction of physical activity [20]. Exercise-based cardiac rehabilitation was developed to reverse the physical deconditioning produced by this restriction of physical activity [21]. Exercise training is central to most cardiac rehabilitation/risk reduction programs. It decreases the risk of coronary artery disease (CAD) [22–25], slows the progression of CAD [26, 27], increases exercise capacity and reduces exercise-induced cardiac ischemia [28].

Different types of exercise have been applied and they come with various protocols in cardiac rehabilitation [29, 30]. Despite this, there is still lack of evidence on which exercise regimen may be ideal for ACS [31]. Therefore, more attention should be paid to verify this.

In this chapter, we will present a brief review of the pathophysiology of acute coronary syndrome and the relationship between exercise and the cardiovascular system. We will also provide an updated discussion of the most relevant discoveries regarding to exercise and its role in managing ACS in clinical studies.

2 Pathophysiology of Acute Coronary Syndrome

Coronary artery disease is characterized by the formation of an atherosclerotic plaque following a long-term and complex process [32]. Most of the time patients would remain asymptomatic if the plaque is stable. Once ruptures, it can cause partial or complete occlusion of a coronary artery. The rupture of plaque exposes the collagen underneath the endothelial, which may result in cascade of platelets activation, leading to thrombus formation [33]. The reduction of blood flow results in these typical angina symptoms [34, 35].

Patients with complete occlusion generally present with STEMI [36]. If the occlusion is unresolved in a timely manner, it may result in transmural infarction [37]. This provides the rationale for early reperfusion with either pharmacological or catheter-based approaches. Patients with partially occluded coronary arteries usually presented with other ST-T changes on EKG. These presentations are grouped as UA or NSTEMI, depending on whether the troponin is elevated or not. Certain anatomic characteristics of the atherosclerotic plaque make it more likely to rupture than others. These include thin fibrous cap, large lipid core populated by numerous inflammatory cells, abundant production of matrix metalloproteinase, and short of smooth muscle cells [33–37]. Plagues with these features are referred to as vulnerable plaque. Such plaques can evade angiographic detection, and may remain silent until they trigger thrombosis [38, 39]. Several factors may make plaque prone to rupture, like systemic inflammatory reactions, local shear stress, platelet hyperactivity, prothrombotic states caused by smoking, dehydration, infection, cocaine, malignancy and so on [37, 40]. Apart from the plaque rupture, vasospasm, dissection or emboli could also jeopardize the hear even in the absence of plaque [32]. In addition, invasive test like the coronaryvessels during percutaneous coronary intervention (PCI) or treatment like coronary artery bypass surgery (CABG) which may also result in myocardial necrosis.

3 Exercise and Cardiovascular System

3.1 Effects of Cardiac Disease on Exercise Performance

Exercise performance may be normal for age and sex in individuals even though they have cardiac disease [41]. However, disease that limits cardiac function may impair exercise capacity. Medications that limit the heart rate response to exercise (such as beta-adrenergic blocking agents) or restrictions in physical activity may also contribute to reduced exercise tolerance in cardiac patients.

3.2 *Effects of Exercise on Cardiovascular System*

Two main kinds of exercise have been used nowadays. They are dynamic exercise and isometric exercise. Dynamic exercise means contraction of muscles with movement at the joint [42]. Blood flow is driven towards skeletal muscle to meet the requirement for metabolism. As a consequence, blood flow is decreased in viscera (Fig. 2.1). Isometric exercise refers to sustained muscle contraction with no change in length of the involved muscle group or joint motion. Unlike dynamic exercise, isometric exercise causes a pressure load on the heart [43] (Fig. 2.2).

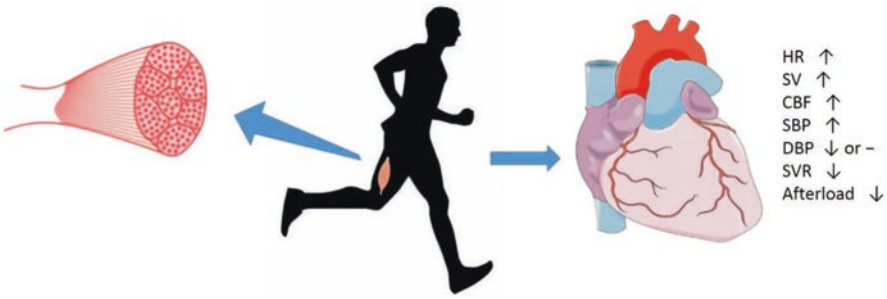

Fig. 2.1 The response of cardiovascular system to dynamic exercise. Dynamic exercise causes a range of cardiovascular responses mediated by activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system. *CBF* coronary blood flow, *DBP* diastolic blood pressure, *HR* heart rate, *SBP* systolic blood pressure, *SV* stroke volume, *SVR* systemic vascular resistance

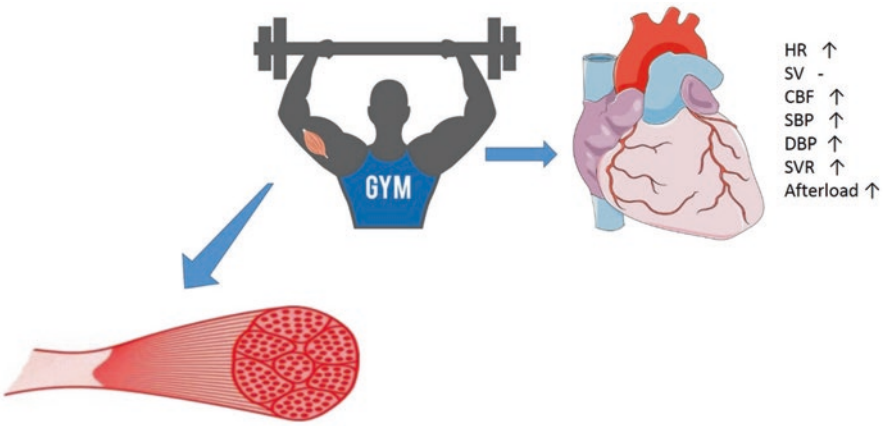

Fig. 2.2 The response of cardiovascular system to isometric exercise. Unlike dynamic exercise, isometric exercise causes no change in SVR and SV, and the increase in cardiac output is primarily driven by the increase in HR. *CBF* coronary blood flow, *DBP* diastolic blood pressure, *HR* heart rate, *SBP* systolic blood pressure, *SV* stroke volume, *SVR* systemic vascular resistance

3.2.1 Biological Effects of Exercise in the Healthy People

Biological Effects of Dynamic Exercise

Dynamic exercise can activate sympathetic nerves and inhibit parasympathetic nerves. This result in an effect of increased in heart rate(HR), systolic blood pressure (SBP), contractility, cardiac output (CO) and stroke volume(SV) [44, 45]. Among these, the increasing stroke volume and cardiac output are the secondary changes. The stroke volume is positively related to the increase in myocardial contractility [46], venous return [47] and decrease in afterload [48]. With these factors, systolic blood pressure increases during dynamic exercise [49]. However, no effect on diastolic blood pressure was observed [44].

Biological Effects of Isometric Exercise

The cardiovascular system response to dynamic and isometric exercise differs. Dynamic exercise causes functional blood congestion in the exercising muscle [50]. This local vasodilatation is limited in isometric exercise due to the sustained mechanical compression of these vessels by the muscle contraction [51]. Both systolic blood pressure and diastolic blood pressure increase in isometric exercise, so as to maintain perfusion of the contracting muscle [50, 52]. Interesting to note, the response of autonomic nervous system to isometric exercise is biphasic, with suppression of the parasympathetic nerves followed by activation of sympathetic nerve [53]. The activation of autonomic nerves stimulates increases in systolic blood pressure, cardiac output, heart rate and diastolic blood pressure. The rise in systolic blood pressure is further driven by an increase in cardiac output [54–57]. The systemic vascular resistance remains unchanged [58] or increases [59]. End diastolic volume does not change and stroke volume remains constant or decreased [60]. Therefore, the increase in cardiac output is primarily driven by an increase in heart rate [61]. With unchanged left ventricular end diastolic pressure and increased cardiac output, it is suggested that isometric exercise is able to precipitate myocardial contractility without following the Frank–Starling mechanism [56].

3.2.2 Biological Effects of Exercise in Coronary Artery Disease

Biological Effects of Dynamic Exercise

As previously discussed, dynamic exercise increases heart rate and systolic blood pressure without affecting the diastolic blood pressure [62, 63]. During dynamic exercise, the dilation of coronary arterioles, noted by a reduction in coronary vascular resistance (CVR), is required to maintain coronary blood flow (CBF) velocity [64]. It has been observed that CBF is increased in subjects with coronary artery disease [65], but not as much as in healthy subjects [46]. In patients with CAD, the

smaller residual vasodilator capacity is, the lower reserve of metabolic adaptation they have [66]. Angina symptoms prone to develop during exercise. It is because the CBF does not meet the demand [46, 67]. Underlying mechanism could be (1) dysfunctional endothelium is unable to produce endothelium-derived factors to cause adequate coronary vasodilatation [68], (2) a reduction in perfusion pressure distal to a significant coronary artery stenosis [66].

Biological Effects of Isometric Exercise

In patients with coronary artery disease, heart rate, mean arterial pressure(MAP) and cardiac output increase like in healthy individuals. However, with the unchanged systemic vascular resistance, patient with CAD less tolerate with volume load than pressure load [61]. As a result, they are at high risk of having ischemic events during isometric exercise than dynamic exercise. CBF increases with isometric exercise in CAD patients [69, 70] but the increase is smaller compared with healthy people [70]. Indeed, coronary vascular resistance decreases in healthy subjects but increases in CAD patients due to coronary vasoconstriction [71].

3.2.3 Biological Effects of Training

Biological Effects of Dynamic Exercise

Regular exercise reduces all-cause mortality, especially cardiovascular morbidity and mortality [22]. Dynamic exercise training improves cardiac adaptation to exercise. Dynamic exercise training can increase maximal cardiac output and total body oxygen consumption [46]. Exercise training can also increases basal parasympathetic nerve activity and lowers circulating catecholamine [72]. Under the effect of parasympathetic nerve system, systemic arterial resistance is decreased, which means a decrease in myocardial oxygen demand for each beat. In patients with coronary artery disease, this may translate into achievement of a higher level of exercise before their ischemic threshold is reached [73]. On the other hand, a lower heart rate reduces systolic duration relative to the duration of a normal cardiac cycle. This result in reduction in systolic compression of intramural coronary vessels and therefore decreases the net impedance to coronary blood flow [46]. Exercise training increases coronary blood flow for the same degree of myocardial work in healthy subjects through a variety of structural and functional adaptations in the coronary circulation [74]. In particular, there appears to be a beneficial effect on arterial endothelial function including attenuation of acetylcholine-driven vasoconstriction, increased nitric oxide production and elevated sensitization of the microvasculature to adenosine-mediated vasodilatation [75]. Furthermore, while training in subjects with CAD has been shown to increase collateral vessel growth, no such phenomenon has been observed in healthy subjects [46].

Biological Effects of Isometric Exercise Training

Isometric exercise training does not increase volume load and the cardiovascular adaptations are different to those seen with dynamic exercise [43]. Also, isometric training does little to improve aerobic capacity or cardiovascular efficiency [76], and no significant sustained changes in stroke volume nor cardiac output have been observed [77, 78]. However, isometric training does lower resting blood pressure. Although the mechanism is unclear [79]. It is hypothesized that sympathetic nervous system, systemic vascular resistance and oxidative stress may be involved [80].

4 Exercise and Acute Coronary Syndrome

4.1 General Concept

It is crucial to clarify the difference of physical activity and exercise training. Physical activity and exercise training have different concepts and body movement. Moreover, these tools are applied in different contexts, depending on the purpose chosen by the healthcare team (e.g., physical educator, physiotherapists, nurse, physician). The American College of Sports Medicine (ACSM) has defined physical activity as any body movement performed in response to voluntary muscle contraction that increases energy expenditure [81]. Thus, it is important to understand that winking or shaking are not considered physical activity, even if they are types of body movement. Walking in the park or talking with a friend is considered as physical activity. Because the contraction of leg muscles is voluntary and the energy expenditure increases exponentially from baseline levels. While exercise training means a planned and structured body movement aimed to improve one or more physical capacities. Exercise training has different designs, and can be introduced as, for example, aerobic and strength/resistance exercise, swimming training, yoga, among others, depending on the approach.

The American Heart Association (AHA) describes physical activity as an important treatment tool. Physical activity can be applied to treat a variety of diseases as hypertension, diabetes mellitus type II, obesity. Physical inactivity is strongly associated with coronary artery disease risk factors, morbidity and mortality [82]. What's more, AHA strongly encourages the inclusion of physical activity in the lifestyle changes of patients who aim to decrease coronary artery disease risk [82]. General recommendations recommend that adults should achieve, at least, 150 min of moderate-intensity activity or 75 min of vigorous-intensity activity per week to prevent coronary artery disease [82, 83].

Exercise training is more often used in cardiac rehabilitation for secondary prevention. The effectiveness of exercise training depends on lots of factors like volume, intensity, endurance time, individual difference, etc., and all these factors are

difficult to control in observational studies. Because of this, the epidemiological data is still lacking. However, the effects of exercise training on coronary artery disease risk factors are widely elucidated in clinical trials, experimental studies and observational studies (i.e., cross-sectional). Exercise training has been demonstrated to improve exercise tolerance, quality of life, functional capacities and job-related physical tasks, as well as decrease cardiovascular risk factors and cardiac mortality [84]. For now, it become a consensus that exercise training should compose the rehabilitation programs of cardiac patients.

4.2 Exercise in Angina Pectoris

The mainstay treatment of angina pectoris is medication, percutaneous transluminal coronary angioplasty (PCI) or coronary artery bypass grafting (CABG). With rare exceptions, much of the evidence that exercise training enhances effort tolerance in patients with angina pectoris could be obtained [85]. Exercise training eliminates angina symptoms by at least two mechanisms. First, it increases VO_2max, thereby reducing the heart rate and systolic blood pressure in response to submaximal exercise. Second, exercise training improves endothelial function [86]. Normal functioning endothelial system is crucial for compensating blood flow in response to stress. During exercise, normal coronary arteries is able to dilate, whereas atherosclerotic coronary arteries often fail to do so because of endothelial dysfunction [86].

Physical activity is negatively associated with the severity of disease. A total of 2172 patients with ACS were enrolled into the study (1649 men and 523 women). Among them, 764 patients (35%) were diagnosed as having unstable angina pectoris. This study proved that physical activity was associated with a reduction of in-hospital mortality. It appears that an active lifestyle may confer protection during the first month after the attack, in terms of both mortality and re-hospitalization due to a recurrent event. Also, this study found out that instead of CK-MB level, troponin I was highly related to physical activity status [87, 88].

Other studies revealed a revised endothelial activity after exercise training [21, 89, 90]. Previously, exercise training is commonly applied in patients with angina who are not candidate for coronary interventions. Results of a clinical trial opposed this. A total of 101 men 70 years old or younger were randomly assigned to 1 year of exercise training or to percutaneous transluminal coronary angioplasty (PTCA). Patients in exercise training group underwent 6 daily 10-min sessions performed at 70% maximal heart rate, followed by daily 20-min home bicycle sessions plus a weekly 60-min supervised session. The exercise level at the onset of ischemia increased 30% in the exercise trained subjects and 20% in the PTCA subjects. Although differences were not significant, but the increase in maximal exercise capacity (20% vs. 0%) and VO_2max (16% vs. 2%) were significantly greater in the exercise-trained subjects. At 1 year follow up, 88% of the PCI subjects versus only 70% of the exercise-trained subjects experienced major cardiovascular events

including myocardial infarction, stroke, revascularization procedure, or hospitalization for angina ($P = 0.023$) [85].

4.3 Exercise in Myocardial Infarction

It was demonstrated that adherence to exercise at 30 days after acute coronary syndrome is associated with a substantially lower rate of short-term major cardiovascular events and all-cause mortality [91]. This study included 18,809 patients from 41 countries enrolled in five randomized clinical trial of the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS). Adherers to diet and exercise had a 50% lower risk for all major events in 6 months compared with no adherers. The risk associated with diet alone or exercise alone was similar for myocardial infarction and stroke, but for death, exercise may have more significant effect. Diet and exercise adherence was associated with a decreased risk of myocardial infarction compared with no adherence.

Promotion of collateral growth is one of the effective therapeutic strategies in patients with myocardial infarction. Physical exercise plays a fundamental role in arteriogenesis. It increase cardiac output, elevates the coronary flow along the arterial branches, thus improves collateral function [92, 93].

A phenomenon that attenuation of myocardial ischemia with an associated increase in ischemic threshold in patients with repeated ischemic episodes was observed in the 1990s. This has later was recognized as ischemic preconditioning (IPC). Induced by repeated bouts of exercise, IPC has been shown to induce a decrease in mean maximal ST depression and ischemia duration on subsequent exercise [94].

Interesting to note, traditional cardiovascular biomarkers (cTnT, hs-cTnT, BNP, NT-proBNP, and d-dimer) and echocardiogram are prone to alterations due to strenuous exercise. In this circumstance, it is important to take previous physical exercise into consideration when ACS is suspected [95].

4.4 Exercise-Based Cardiac Rehabilitation

4.4.1 Historical Perspective

Cardiac rehabilitation generates secondary prevention of CAD and is an essential component of care for all cardiac patients [96, 97]. It consists of medical, physical, social and psychological intervention. It favorably influences the underlying risk factors in order to stabilize, slow and even reverse disease progression. Therefore cardiac rehabilitation facilitates the ability of the patient to preserve or resume an active and functional contribution to the community [98, 99]. Cardiac rehabilitation promotes quality of life through increasing cardiac function and exercise tolerance,

improving cardiovascular symptoms, reducing levels of anxiety, depression and stress, and maintaining independence in activities of daily living [97, 99, 100].

Shorter hospitalizations, along with effective medications and procedures have changed cardiac rehabilitation program. Nowadays, exercise training, physical well-being counseling, medication compliance and diet are key components of the rehabilitation [82]. U.S. Centers for Medicare & Medicaid Services (CMS) guidelines reflect these changes and stipulate that "cardiac rehabilitation programs must be comprehensive and…include a medical evaluation, a program to modify cardiac risk factors…prescribed exercise, education, and counseling." Consequently, cardiac rehabilitation programs are now often referred to as "cardiac rehabilitation/secondary prevention programs". The American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) recommend comprehensive cardiac rehabilitation programs for patients who have undergone percutaneous transluminal coronary angioplasty (PTCA), CABG, post ACS, stable angina or peripheral vascular disease [101]. This recommendation has the highest level of evidence (level A) for all conditions except angina (level B) [101]. The Centers for Medicare & Medicaid Services also defines comprehensive cardiac rehabilitation "reasonable and necessary" for patients after valve surgery and heart or heart and lung transplantation [102]. They proposed using referral to cardiac rehabilitation as a core performance measurement for the management of patients with coronary disease and after cardiac surgery starting in January 2014, with an impact on hospital reimbursement in 2015 [103]. Consequently, interest in cardiac rehabilitation will increase in the near future [104].

Structured exercise has been identified as being central to the success of cardiac rehabilitation [105–107]. Back in the early 1950s, exercise was not advised in MI patient. In contrast to traditional concepts, increasing evidence has shown that exercise have beneficial effects on cardiovascular system. Exercised-based cardiac rehabilitation has gradually come into view and has developed to reverse the restriction of physical activity. Exercise training is central to most cardiac rehabilitation/risk reduction programs because it increases exercise capacity and reduces exercise-induced angina. In addition, exercise training is one of the few prevention techniques that reduce angina in the time before beta-adrenergic blocking agents and coronary artery revascularization procedures [21]. Nevertheless, some studies argues against the protective effect of exercise training. A meta-analysis including 21,295 patients with CAD noted the reductions in mortality and recurrent myocardial infarction were similar for programs that involved exercise and programs that do not [28].

4.4.2 Effect of Exercised-Based Cardiac Rehabilitation on Patients with Acute Coronary Syndrome

Exercise-based cardiac rehab improves mortality and decrease readmission after ACS. A total of 10,794 patients with myocardial infarction, CABG, PTCA and angina were randomly assigned to exercise-based cardiac rehabilitation or usual

care. At 12 month follow-up, total mortality and cardiovascular mortality were 13% and 26% lower respectively compared to usual care group. Meanwhile, hospital admissions were 31% lower in the first year of the study ($P < 0.05$ for all). Subsequent MI, CABG, or PTCA did not change [106]. A variety of secondary prevention programs, including those without an exercise component, can obtain similar results [98].

Aerobic endurance training is fundamental for exercise-centered rehab program [108]. It improves cardiorespiratory fitness and functional capacity, reduces disease-related symptoms and favorably influences coronary risk factors [109, 110].

PTCA has been recognized as the most effective treatment for ACS [111, 112]. A retrospective analysis of 2395 patients after PTCA noted an approximately 45% reduction in mortality ($P < 0.001$) in the 40% of patients who participated in exercised-based cardiac rehabilitation. What's more, the reduction in mortality did not differ by sex, age, or PTCA urgency. Therefore, this suggests that cardiac rehabilitation can benefit almost all patients after PTCA [107]. Although selection bias cannot be ruled out, the overwhelming beneficial effect from cardiac rehab remains promising (Table 2.1).

5 Conclusion

It has been established that exercise was crucial for both prevention and recovery in patients with CAD [113–120]. Recent studies have shed light on the mechanisms that may responsible for cardiac alterations after ACS and the beneficial adaptations promoted by exercise [121–125]. In spite that majority of studies have proved the protective effect of exercise ACS, problems still exist in interpretation. Regarding the effect of prevention, exercise have the potential to act by pre-conditioning the heart to ischemic [126–128]. IPC has been found to exert its protective effect in a two phase manner [129–131]: the classic or early pre-conditioning that lasts for about 3 h after the exercise bout, and the late pre-conditioning, or "second window of protection," which begins approximately a day later, and may last up to 72 h. The underlying explanation to this could be increased expression and synthesis of cyto-protective factors. It is not easy to detect the cardio protective effect of the short-lived early IPC in clinical application [130] since there is no way to predict the occurrence of ACS yet. The second window may at least in part explain the reduced severity of myocardial damage during ACS, as evidenced in the physically active subjects in the study [130, 132]. It is not known yet whether the cardio protective effects of physical activity status may have more lasting effects to favourably impact short-term prognosis during recovery from an acute coronary syndrome [133]. Alternatively, the reduced severity of myocardial necrosis observed in the physically active individuals may be the main factor for a better prognosis at the recovery period [134]. Based on this, it is reasonable to assume that revascularization therapies may be more effective in a less damaged myocardium [135, 136], such as in the case of physically active individuals [137].

Table 2.1 Benefits of exercise in acute coronary syndrome

Benefits	Change
Improvement in exercise capacity	
Estimated metabolic equivalents	↑
Peak oxygen consumption	↑
Peak anaerobic threshold	↑
Improvement in lipid profiles	
Total cholesterol	↓
Triglycerides	↓
HDL-C	↑(higher in patients with low baseline)
LDL-C	↓
LDL-C/HDL-C	↓(higher in certain subgroups)
Reduction in inflammation	
hs-CRP	↓
Reduction in indices of obesity	
BMI	↓
Fat	↓
Metabolic syndrome	↓
Improvements in behavioural characteristics	
Depression	
Anxiety	
Hostility	
Somatization	
Overall psychological distress	
Reduction in stress-related increased mortality	
Improvements in quality of life and components	
Improvement in autonomic tone	
Increased heart rate recovery	
Increased heart rate variability	
Reduced resting pulse	
Improvements in blood rheology	
Improvements in social benefits	
Reduction in hospitalization costs	
Reduction in major morbidity and mortality	

BMI body mass index, *hs-CRP* high-sensitive C-reactive protein, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoproteincholesterol

As for the effect of treatment and recovery, The major problem with exercise-based cardiac rehabilitation currently is its underutilization [138, 139]. Only 14–35% of MI survivors and approximately 31% of patients after PCI were referred to cardiac rehabilitation programs [140]. Women, elderly, and minorities—the very groups at greatest risk for recurrent events—have especially low referral rates [141,

142]. Physician endorsement of cardiac rehabilitation is one of the most important predictors of participation. The possible causes of the low referral rates could be: (1) underestimating the benefit of exercise; (2) health professionals' lack of knowledge on exercise training; (3) absence of exercise training propagation; (4) lack of a conclusive clinical trial [143–147]. Besides, in some circumstances, individual compliance contribute a lot to the successful of rehab. Physician referral will probably increase when such action becomes a core measure of hospital performance. Including an automatic referral to cardiac rehabilitation in standardized order sets for qualified patients is among the best ways to solve the problem [148, 149]. On the other hand, if Medicare adopts the referral to exercise-based rehab as one of the performances measurement for patient's management, not only the referral rate would be increased, but also the medical care costs would be controlled [150]. Although current data supporting the benefits of exercise-based treatment are highly regarded, standard-powered clinical trial remains insufficient. Most of the evidence were provide by meta-analysis, of which publication bias is inevitable. Also, many of the trials evaluated in the available meta-analyses included studies that predate the present aggressive medical and interventional therapy [151], thus make the conclusion more obscure. Because of this, payers may reluctant to reimburse exercise-based treatment, even though this outcome seems unlikely given Medicare's present evaluation of these data [152]. As the other way around, since the cost of the interventional procedure is huge, cost-effective management like exercise-based treatment and risk reduction programs may be applied before proceeding to pricy ones. Such a change seems impossible in the present fee-for-service model. Given the available comparison of medical versus invasive strategies, it is still realistic [153–156].

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Chapter 3
Exercise-Based Rehabilitation for Heart Failure: Clinical Evidence

Rongjing Ding

Abstract People with heart failure experience marked reduction in their exercise capacity which has detrimental effects on their activities of daily living, health-related quality of life, and ultimately their hospital ad-mission rate and mortality. Numerous cardiac rehabilitation studies have demonstrated functional benefits, improvement in quality of life and clinical outcomes from exercise training in patients with HFrEF. Based on evidences, the American College of Cardiology/American Heart Association, European Society of Cardiology, and National Institute for Health and Care Excellence(NICE) consistently recommend exercise-based cardiac rehabilitation(CR) as an effective and safe adjunct for patients with stable class II to III heart failure (HF) who do not have advanced arrhythmias and who do not have other limitations to exercise. This recommendation applies to patients with HFrEF as well as to patients with HFpEF besides patients with class IV HF, although the data are not as robust for patients with HFpEF. In this article, the clinical evidence on effects of exercise for HFrEF and HFpEF as well as end-stage heart failure were separately reviewed.

Keywords Exercise • Rehabilitation • Heart failure

Heart failure (HF) is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. HF may be caused by disease of the myocardium, pericardium, endocardium, heart valves, vessels, or by metabolic disorders [1]. HF due to left ventricular dysfunction is categorized according to left ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (with LVEF ≤40%, known as HFrEF) and HF with preserved ejection fraction (with LVEF ≥ 50%; known as HFpEF). The diagnosis of HFpEF is challenging. Several different criteria have been used to further define HFpEF. Patients with an EF in the range of 40–50% represent an intermediate group

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or median range named borderline HFpEF[1] or HfmrEF [2]. Despite the advance of medication and mechanical treatment in heart failure, a meta-analysis reported a mortality of 32% in HFPEF (ejection fraction >35–50%) versus 41% mortality in HFREF (relative risk (RR) 0.79) over an average of 47 months follow-up [3]. People with heart failure experience marked reduction in their exercise capacity which has detrimental effects on their activities of daily living, health-related quality of life, and ultimately their hospital admission rate and mortality [4]. Numerous cardiac rehabilitation studies have demonstrated functional benefits, improvement in quality of life and clinical outcomes from exercise training in patients with HFrEF. Based on evidences, The American College of Cardiology/American Heart Association, European Society of Cardiology, and National Institute for Health and Care Excellence(NICE) consistently recommend exercise-based cardiac rehabilitation(CR) as an effective and safe adjunct for patients with stable class II to III heart failure (HF) who do not have advanced arrhythmias and who do not have other limitations to exercise [1, 5]. This recommendation applies to patients with HFrEF as well as to patients with HFpEF besides patients with class IV HF, although the data are not as robust for patients with HFpEF.

1 Exercise Prescription

In cardiac rehabilitation programs for patients with HF, the most effective exercises for physical conditioning is aerobic exercise training since evidence and experience is greatest for this type of activity. There are other exercise modalities include resistive training and inspiratory muscle training sometimes used in patients with HF. An appropriate exercise prescription, in parallel with a medication prescription, includes intensity (dose), duration (how long for each session), frequency (usually on a weekly basis), location (center- or home-based), type of activity, and very importantly, progression. Intensity can be specified as a heart rate, or a rated perceived exertion scale (RPE). Although there are no reports of adverse events directly associated with exercise training in CHF patients, it is advisable to initiate the training program in a supervised setting, where the training program in a supervised setting, where individual responses to physical activity can be observed and modified accordingly. Once a safe and effective level of training has been established, most patients can be advanced to a combined supervised and nonsupervised program.

2 Evidence on Effects of Exercise

Most of the studies on exercise in HF have included patients with HfrEF [6]. Much less data are available on patients with HFpEF, although these patients can be as limited in their exercise capacity as those with HfrEF [7]. Thus we separately reviewed the evidence on effects of exercise for HFrEF and HFpEF.

2.1 For Heart Failure with Reduced Ejection Fraction

2.1.1 Aerobic Training

Effect on Hemodynamics

In the late 1980s, Sullivan and coworkers from Duke University published the first reports of their experience with training patients with HF. This study showed a significant improvement in exercise tolerance, as evidenced by an increase in exercise duration and peak oxygen intake (VO2peak) [8, 9]. The first larger prospective randomized study to provide evidence for a training-induced reverse remodeling came from Hambrecht and colleagues [10], who demonstrated that endurance training led to reverse left ventricular(LV)remodeling, with modest improvements in EF from 30 to 35% (LVEF; weighted mean difference 2.6%) as well as reductions of LV end-diastolic diameter(weighted mean difference − 11.5 mL and −12.9 mL, respectively). In the largest included trial, HF ACTION, 2331 patients with reduced LVEF (≤35%) and NYHA class II to IV HF were randomly assigned to a formal exercise program versus a control program [11]. The peak improvement in peak VO2 was modest, though statistically significant (0.6 versus 0.2 mL/min/kg in controls) both at 3 and 12 months, as was the improvement in 6-min walk distance at 3 months. The 6-min walk improvement at 3 months was attenuated at 12 months.

The results of 2 meta-analyses in 2007 [12] and 2012 [13] which included these studies showed that aerobic training, especially greater than 6 months' duration, significantly reversed LV remodeling, whereas strength training alone or combined with aerobic training had no effect on reverse remodeling.

Effect on Skeletal Muscle

It was previously thought that exercise limitation in patient with HF was due entirely to cardiac dysfunction. However, drugs that improve cardiac output may not acutely improve exercise tolerance [14–17]. Thus factors in addition to the low cardiac output and reduced skeletal muscle blood flow may contribute to poor exercise tolerance and fatigue. Muscle biopsies in patients with HF show a decrease in slow-twitch type I fibers, an increase in fast-twitch type IIb fibers, and a decrease in the oxidative enzymes succinate dehydrogenase and citrate synthetase [8, 9]. Cardiac cachexia, the most extreme form of muscle wasting that occurs in CHF, there are increased levels of norepinephrine, human growth hormone, insulin, and tumor necrosis factor (TNF-α), all of which may play a role in muscle wasting of lesser degree [18, 19]. In addition, skeletal muscle utilizes high-energy phosphates in an inefficient manner; as a result, lactic acid accumulates at a more rapid rate than in normal controls, contributing to muscle fatigue and limited exercise capacity. Skeletal muscle dysfunction can also involve the respiratory muscles, which may contribute to fatigue and dyspnea on exertion [20]. The importance of skeletal muscle dysfunction provides part of the rationale for the use of cardiac rehabilitation in patients with HF.

A number of exercise training studies have shown that these abnormalities can at least be partially reversed. Belardinelli and colleagues reported that low-intensity(below anaerobic threshold)exercise training program on a group of HF patients increased patients VO2peak and decreased submaximal work lactate levels, but there was no change in resting or exercise hemodynamics, indicating that the origin of the changes are in the periphery [21]. Muscle histology revealed an increase in fiber size and mitochondrial volume density, with a high correlation between changes in the latter and changes in VO2peak and anaerobic threshold [21]. Stratton et al. and Hambrecht et al. separately demonstrated that a increase in exercise duration accompanied by higher muscle PH at submaximal workloads and a reduced depletion as well as more raped resythesis of physphocreatine [22, 23].

Exercise training can increase muscle oxidative capacity and reduces oxidative stress. In patients with HFrEF, exercise training improves oxygen utilization with increased activity of oxidative enzymes and an increase in mitochondrial content [24]. Such exercise-induced changes may improve the peak VO2 and delay the onset of anaerobic metabolism. Patients with the worse function seem to benefit the most.

Health-Related Quality of Life

Health-related quality of life has been considered another very important outcome besides mortality. The majority of HF studies reported disease-specific quality of life using the Minnesota Living with Heart failure questionnaire(MLWHF) and Kansas City Cardiomyopathy Qusestionnaire(KCCQ), generic HRQoL using the EuroQoL(EQ-5D), SF-36, Psychological General Wellbeing index(PGWB),Patient's Global Assessment of Quality of Life(PGAQol) and Spritzer's Quality of Life Index(QLI). A meta-analysis with 19 randomized controlled trials compared the health-related quality of life between exercise training and usual care in a total of 4740 patients with NYHA functional classes II and III HF (predominantly HFrEF) [25]. There was no study in 19 trials reported lower HRQoL score in people who exercised compared with controls. 11 trials (58%) reported higher HRQoL score in exercise group compared with control. When pooled across all studies, there was significantly higher HRQoL score with exercise regardless of the HROoL measure used (19 trials[21 comparisions], 95%CI-0.66 to −0.26; P value < 0.0001). Pooling across13 trials of 1270 participants found clinically significant improvement regarding MLSHF score up to 12 months' follow-up in exercise group (95% CI-9.2 to −2.4; P value = 0.0007). Another 3 trials reported higher MLWHF score at follow-up greater than 12 months in exercise group compared with control (95%CI-17.5 to −1.5; P value <0.0001).

Psychological Factor

Depression is common among patients with HF and adversely impacts prognosis [26]. The largest included trial was the HF-ACTION trial in which the Beck Depression Inventory II was administered to 2322 patients [27]. At entry, 28% of patients had scores of 14 or higher, which is considered clinically significant. Exercise training modestly improved the depression scores compared to the control group at 3 months with a smaller response at 1 year. A meta-analysis of 16 randomized trials with 3226 patients with HF (mostly HFrEF) found that exercise training reduced symptoms of depression and this antidepressive effect was consistent in patients under and over 65 years of age [28].

Mortality and Hospital Readmission

The first prospective randomized study to provide evidence for a training-induced decrease HF patients mortality and hospital readmission came from Belardinelli and colleagues [29]. Total 99 Subjects recruited in this study and 50 subjects were assigned to do exercise on the cycle ergometer at 60% VO2peak for up to 1 years. Both VO2peak and thallium activity score improved at 8 weeks(18% and 24%, respectively). Follow-up continued for approximately 3 years, during which time there were 9 deaths(all cardiac) and 5 hospital readmissions for heart failure in the trained group compared with 20 and 14, respectively, in the controls(relative risk = 0.37, p = 0.01, and relative risk = 0.29, p = 0.02, respectively).

The most recent meta-analysis included 33 randomized controlled trials comparing exercise training and usual care in a total of 4740 patients with NYHA functional classes II and III HF (predominantly HFrEF) [25]. Among 33 randomized studies of 4740 participants, 15 trials of 1328 participants and 12 trials of 1036 participants reported overall hospital admission and HF-specific admissions respectively up to 12 months' follow-up. The rate of overall (RR 0.75,95% CI 0.62 to 0.92; P value = 0.005) and HF-specific admissions(RR 0.61;95% CI 0.46 to 0.80; P value = 0.002) were significantly lower in exercise training group compared with control. 5 trials reported overall hospital admissions with more than 12 months' follow-up and found no difference compared exercise group with control group(RR 0.92;95% CI 0.66 to 1.29; P value = 0.63).

The effect of exercise on All-cause mortality in patients with HF was investigated in 25 studies of 1871 participants at up to 12-months' follow-up and found no significant difference in pooled mortality compared exercise with control(Risk Ratio (RR) 0.93;95% CI 0.69 to 1.27; p value = 0.59). However, when extend the longer follow-up to more 12 months, a trend towards a reduction in all-cause mortality was found in 6 trials of 2845 participants (RR 0.88; 95%CI 0.75 to 1.02; P value = 0.07).

Cost-Effectiveness Analysis

Cost-effectiveness analysis has been regarded as a very important issue when investigated the benefit of exercise training on HF. The most recent meta-analysis included 33 randomized controlled trials comparing exercise training and usual care in a total of 4740 patients with NYHA functional classes II and III HF (predominantly HFrEF) [25]. Among 33 randomized studies of 4740 participants, 3 randomized studies reported economic data. Using exponential survival modeling to 15.5 years, there was an incremental cost-effectiveness ration of USD1773/life-year saved in HF patients with exercise compared with control and the estimated increment in life expectancy was 1.82 years/person in HF patients with exercise compared with control. HF ACTION study reported that HF patient will gain mean 0.03 in QALY if each cost USD 1161 at 2.5 years' follow-up(Flynn 2009).It was estimated with 89.9% probability that exercise training was more cost-effective than usual care at a maximum willingness to pay threshold of USD 50,000 in HF ACTION study.

Effect of Intensity and Volume of Aerobic Training

Since the 1980s, many studies have demonstrated the safety and effectiveness of aerobic moderate-intensity continuous exercise(MICE) in patients with HF [25]. In the early days of its use in HF patient, no greater than moderate-intensity training was recommended. Some previous studies found inverse dose-response relationship between physical activity and disease [30–32], that is more vigorous exercise can be performed on fewer days and got the same health benefit compared with moderate intensity exercise.

High intensity intermittent exercise(HIIE) involves the use of short periods of exercise interspersed with rest periods. The duration and intensity of the exercise and rest can be varied in numerous ways. In a study of more than 5000 healthy men and women, relative exercise training intensity was more important than duration in reducing the risk of all-cause and coronary heart disease mortality [33]. Recently clinicians and researchers have begun to investigate HIIE training as an intervention for HF patients.

High-intensity training may provide some advantages over moderate intensity training but evidence is limited. A randomized trial enrolling 27 patients with stable post-infarction chronic HF found that high-intensity aerobic interval training (four intermittent 40-min intervals at up to 95% of peak heart rate) resulted in a 46% increase in Vo2peak for those performing HIIE compared with a 14% increase for those performing MICE (at 70% of peak heart rate; 45 versus 14% increase).This study also demonstrated that all measures of LV systolic and diastolic function were significantly improved after HIIE but not MICE [24]. Freyssin and colleagues [34] used an 8-week HIIE program, which resulted in a 27% increase in Vo2peak. In a study by FU and colleagues [35], patients with HF undergoing an HIIE program for 12 weeks had a 22% increase in Vo2peak. Only the group participating in HIIE had

significant improvements in CO as well as LV ejection fraction. Chrysohoou and colleagues [36] looked at the effect of 12 weeks HIIE training and demonstrated a 31% improvement in Vo2peak. In a 16-week program comparing HIIE to MICE training, Smart and Steele [37] reported a significant increase (21%) only in the HIIE group. But reported no significant improvements for patients performing 16 weeks of HIIE or MICE training in LV ejection fraction, end-systolic and end-diastolic volume, and systolic and diastolic velocities. A meta-analysis including seven randomized trials comparing high-intensity training to moderate-intensity continuous training in clinically stable patients with HFrEF found greater improvements in exercise tolerance with high-intensity training but no significant effect on LVEF at rest [38]. A systematic review suggested that higher-intensity training in patients with HF may have a greater beneficial effect on peak oxygen consumption [39]. All data now support the usage of HIIE on HF patients, but there are still some questions need to be answered, such as how to choose the intensity, how to choose the frequency, how to choose the duration, how to evaluate the benefit and risk.

2.1.2 Resistive Training

Resistive training (RT) includes isotonic exercise and isometric exercise. Isotonic (dynamic)exercise, which causes movement of the limb, is also further classified as either concentric(shortening of the muscle fibers, which is the most common type of muscle action) or eccentric(lengthening of the muscle fibers such as might occur when a weight is lowered against gravity). Isometric (static) exercise results in no movement of the limb. The extent to which an activity is predominantly aerobic or anaerobic depends primarily on its intensity relative to the person's capacity for that type of exercise.

During isometric exercise, increases in HR and both SBP and DBP are nearly proportional to the force exerted relative to the greatest possible force that an individual can evoke(percent maximum voluntary contraction [MVC]) rather than the absolute tension developed. Stroke volume remains largely unchanged except at high levels of tension (>50% MVC), where in it may decrease for the Valsava maneuver below. The result is a moderate increase in cardiac output, with little increase in VO2. Despite the increased cardiac output, blood flow to the noncontracting muscles does not significantly increase, probably because of reflex casoconstriction. At an MVC > =20–30%, the intramuscular pressure exceeds the intravascular pressure in the contracting muscles and significantly reduces localized blood flow, causing muscle ischemia and hypoxia. The combination of vasoconstriction and increased cardiac output results in a disproportionate rise in SBP, DBP, mean BP, and peripheral vascular resistance [40, 41]. Comparison of effects of Aerobic endurance training with strength training on health and fitness variables see Table 3.1 [42].

In patients with HF, despite well-described abnormalities of skeletal muscle [43], RT traditionally has been discouraged because of concerns for furthering impairment of LV function and potential adverse LV remodeling related to increased

Table 3.1 Comparison of effects of aerobic endurance training with strength training on health and fitness variables ↑ indicates values increase; ↓, values decrease; 0, values remain unchanged; 1 arrow, small effect; 2 arrows, moderate effect; 3 arrows, large effect; *HDL* high-density lipoprotain cholesterol, *LDL* low-density lipoprotein cholesterol

Variable	Aerobic exercise	Resistance exercise
Body composition		
Bone mineral density	↑ ↑	↑ ↑
Percent body fat	↓ ↓	↓
Lean body mass	0	↑ ↑
Muscle strength	0 ↑	↑ ↑ ↑
Glucose metabolism		
Insulin response to glucose challenge	↓ ↓	↓ ↓
Basal insulin levels	↓	↓
Insulin sensitivity	↑ ↑	↑ ↑
Plasma lipids and lipoproteins		
HDL cholesterol	↑ 0	↑ 0
LDL cholesterol	↓ 0	↓ 0
Triglycarides	↓ ↓	↓ 0
Cardiovascular dynamics		
Resting heart rate	↓ ↓	0
Stroke volume, resting and maximal	↑ ↑	0
Cardiac output, rest	0	0
Cardiac output, maximal	↑ ↑	0
SBP at rest	↓ 0	0
DBP at rest	↓ 0	0
Vo_2max	↑ ↑ ↑	↑ 0
Submaximal and maximal endurance time	↑ ↑ ↑	↑ ↑
Submaximal exercise rate-pressure product	↓ ↓ ↓	↓ ↓
Basal metabolic rate	↑ 0	↑
Health-related quality of life	↑ 0	↑ 0

afterload during the lifting phase. In practice, the hemodynamic responses performed by patients with HF at the intensity of RT do not exceed levels attained during standard exercise testing [44], and no adverse remodeling after RT were reported [45]. Thus, clinical practice supported that RT can be incorporated safely into rehabilitation programs for patients with HF, although further study of this important area is needed [46, 47]. In older women with HF randomized to 10 weeks of RT or control, the former was associated with a 43% increase in muscle strength and a 49% increase in 6-min walk distance, along with a 299% increase in submaximal endurance measured by the number of lifts at an intensity of 90% of baseline 1-repetition maximum(the maximum weight that can be used to complete 1 repetition, 1-RM) [45]. However the total muscle mass in older women with HF was unchanged. Thus, the effects of RT in HF appear to be directed at improving skeletal muscle untrastructural abnormalities and /or neuro- muscular function rather than simply increasing muscle mass.

A small non-randomized study of combined aerobic and resistive training in a group of HF patients demonstrated a drop in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels without any safety concerns or worsening remodeling [48]. Other small studies have reported improvements in muscle structure and vasoreactivity with resistive training [49, 50]. However, a systematic review found that aerobic plus strength training was not more effective than aerobic training alone in terms of VO2max [51]. There is evidence that the benefit of aerobic exercise on left ventricular volumes may be diminished or lost with the addition of strength training [13].So further work in this area is needed.

Decreased skeletal muscle oxidative capacity [52], secondary to reduced mitochondrial density [53, 54] and/or function [55–57], may contribute to exercise intolerance. Studies that combined aerobic-and resistance-training programs in HF patients have shown improved aerobic fitness and muscle strength [58–60] accompanied by improved mitochondrial function [60]. However Michael J. Toth et al. found that HF syndrome has minimal effects on skeletal muscle mitochondrial biology when the confounding effects of muscle disuse and other disease-related factors are removed. Moreover, the beneficial effects of resistance training on physical function in HF patients and controls are likely not related to alterations in mitochondrial biology. Michael J. Toth study indicated that it maybe not the resistance-training component of the program contributes to improvements in mitochondrial biology but improvements are related solely to the aerobic component.

2.1.3 Inspiratory Muscle Training

Respiratory contributions have been shown to limit exercise in patients with heart failure (HF). The abnormalities in ventilation in HF are mostly restrictive in origin, producing a ventilatory response during exercise in HF that is characterized by [61]: (1) decreased tidal volume, end-tidal carbon dioxide, peak oxygen consumption (VO2), and tidal volume to ventilation ratio (VT/VE); and (2) increased respiratory rate, VE, peak dead space ventilation to tidal volume ratio (VD/VT), ventilation to VO2 ratio (VE/VO2), and the VE/carbon dioxide consumption(VE/VCO2) slope. The key factors limiting perfusion in HF include poor right ventricular performance, elevated pulmonary artery pressure, and elevated pulmonary vascular resistance (PVR). A substantial body of literature has identified the relationship that inspiratory muscle weakness has with symptoms, exercise intolerance, inefficient ventilation, and abnormal cardiopulmonary exercise testing(CPX) results [20, 62–64]. A sub Preliminary evidence suggests that inspiratory muscle training (IMT) may improve exercise capacity in patients with chronic HF. There have been 5 systematic reviews examined the role of inspiratory muscle training compared with sham group or control group in HF and the results of each review have been favorable regarding many of the pathophysiologic manifestations of HF [65–69]. Twenty-two studies with a total of 1078 participants included in those reviews. The duration of therapy was 4–12 weeks with 15–30 min per day and 3–7 days per week. Eighteen

of the studies were randomized controlled trials and the other four were quasi-experimental studies. Most IMT studies have been in patients with HFrEF, one study found IMT to be beneficial for patients with HFpEF [70]. The results showed that IMT significantly improved the manifestations of HF included dyspnea, quality of life, balance, peripheral muscle strength and blood flow, peripheral muscle sympathetic nervous activity, heart rate, respiratory rate, peak VO2, 6-min walk test distance, ventilation, VE/VCO2 slope, oxygen uptake efficiency, circulatory power, recovery oxygen kinetics, and several indices of cardiac performance [70]. There was considerable heterogeneity among the studies. Improvements were greater in patients with baseline inspiratory muscle weakness. The one study not observing such an improvement had a small number of subjects in each group (n = 8) and administered IMT for only 15 min, twice daily for 8 weeks at 30% of the maximal inspiratory pressure(MIP) [71].

2.2 For Heart Failure with Preserved Ejection Fraction

Heart Failure with Preserved Ejection Fraction (HFpEF) is defined as an inability of the ventricles to optimally accept blood from the atria with blunted end diastolic volume response by limiting the stroke volume and cardiac output. HFpEF prevalence is higher in elderly and women and may be linked to hypertension, diabetes mellitus and atrial fibrillation [72, 73]. Exercise intolerance and reduced quality of life are known as the primary chronic symptoms in HFpEF patients. Left ventricular (LV) diastolic dysfunction has been identified as one of the mechanisms underlying exercise intolerance in these patients [74].

Conventional methods for treating heart failure have proven largely ineffective for HFpEF patients [72, 75–77]. Several recent studies have evaluated exercise training as a therapeutic management strategy in patients with HFPEF [78–83] which have demonstrated a variable degree of improvement in exercise tolerance and diastolic function in response to training. Recently, a meta-analysis published by Ambarish pandey in 2015, included six randomized controlled trials (see Table 3.2) of exercise training in 276 patients with HfpEF [84]. Exercise training improved cardiorespiratory fitness (CRF) (ml/kg per min; weighted mean difference, 2.72;95% confidence interval, 1.79–3.65) and quality of life (estimated using Minnesota living with heart failure questionnaire(MLHFQ); weighted mean difference,−3.97;95% confidence interval, −7.21 to −0.72) when compared with the control group. But ejection fraction and a measure of diastolic function (E/A ratio) were not significantly changed.

However, another meta-analysis published by Gudrun Dieberg et al. in 2015 has somewhat different results [85]. The Gudrun meta-analysis included 7 trials (see Table 3.3) a total of 258 participants with HFpEF. Both meta-analysis found similar benefits regarding CRF and quality of life(including MLHFQ and short form 36 health survey(SF-36)), but only Gudrun et al. found exercise benefit on diastolic function and V_E/VCO2 slope. The corresponding data for V_E/VCO2 slope MD

Table 3.2 Control and exercise group interventions used in the studies included in the Meta-analysis

	Exercise training group intervention	Control group intervention	Duration (weeks)	Outcome measured
Gary et al.	Self-monitored community based walking intervention + home education program.	Weekly visits with home education program	12	Exercise capacity as 6-min walk test
	Walking intervention with ambulatory heart rate monitoring, initially at an intensity of 40% of target heart rate for wk. 1 with gradual increase to 60% as tolerated			Quality of life
Kitzman et al.	Supervised endurance training (track walking + cycling) 3× per wk.	Telephone call follow-up every 2 weeks without addressing exercise behavior	16	Peak oxygen uptake
	Wk 1–2: Exercise at 40–50% of peak Vo_2 with gradually increasing duration			Systolic, diastolic function by echo
	Wk 3–16: Exercise intensity at 60–70% of peak Vo_2 and duration increased to 15–20 min			LV dimensions
				Quality of life
Edelmann et al.	Supervised, endurance (cycling) + resistance training	Usual care and maintenance of usual activities	24	Peak oxygen uptake
	Wk 1–4: Aerobic endurance training at 50–60% of baseline peak Vo_2			Systolic, diastolic function by echo
	Wk 5–12: Aerobic endurance at 70% of baseline peak			
	Vo_2 + resistance training			LV dimensions
				Quality of life
Alves et al.	Supervised endurance training on treadmill/cycle ergometer	Usual care with regular cardiologist follow-up	24	Peak oxygen uptake
	Wk 1–4: Training at 70–75% of peak Vo_2			Systolic, diastolic function by echo
	Wk 5–24: Training at 70–75% of peak Vo_2			LV dimensions
				Quality of life
Smart et al.	Supervised, outpatient, cycle ergometer exercise training	Usual care and maintenance of usual activity levels	16	Peak oxygen uptake
	Initial intensity of 60–70% peak Vo_2			Systolic, diastolic function by echo
	Exercise intensity uptitrated by 2–5 W/week as tolerated			LV dimensions
				Quality of life

LV indicates left ventricle; and Peak Vo_2 peak oxygen uptake

Table 3.3 Patient and training characteristics for randomized control trials included in the Meta-analysis on exercise training studies with HFpEF patients

Study	Country	Sessions attended (%)	Participants include in the final analysis	Training characteristics	Outcomes measusres
Alves (2012)	Portugal	100	Total patients N = 98	6 months of interval exercise training. First month, 3 sessions per week, and 15 min at 70–75% of maximal heart rate. Following 5 months. 3 sessions per week, and 35 min at 70–75% of maximal heart rate	LVEF
			Exercise (>55%): n = 20, 22 m/9f, mean age 62.9. Control group n = 11 exercise control (45–54%): n = 23, 24 m/9f, mean age 63.6. Control group n = 10, exercise control (<45%): n = 22, 27 m/7f, mean age 62.0. Control group n = 12		Diastolic function
			NYHA class I/II/III/IV		
Edelmann (2011)	Germany	34 – Exercise training group participated in >90%, 52 in 70–90% and 14% in 70% of the exercise sessions	Total patients N = 64	32 sessions of continuous exercise training. Weeks 1–4, 2 sessions per week. 20–40 min of 50–60% of peak VO_2. Week 5 onward, 3 sessions per week at 70% of peak VO_2 and resistance training, 15 reps at 60–65% 1RM	LVEF
			Exercise: n = 44, 24 m/20f, mean age 64. Exercise control: n = 20, 12 m/8f, mean age 65		Peak VO_2
			NYHA class II/III		Heart rate
					6MWT
					MLHF
					SF36
Gary (2004)	USA	100	Total patients N = 28	12 weeks of continuous exercise training (walking). 3 sessions per week, 20–40 min at 40–60% of the maximal heart rate	6MWT
			Exercise: n = 15, 15f, mean age 67. Control: n = 13, 13f, mean age 69		MLHF
			NYHA class II/III		

(continued)

Table 3.3 (continued)

Study	Country	Sessions attended (%)	Participants include in the final analysis	Training characteristics	Outcomes measusres
Karavidas (2013)	Greece	100	Total patients N = 30	6 weeks of functional electrical stimulation (FES) training. 5 sessions per week, 30 min of 25 Hz for 5 s followed by 5 s rest	MLHF
			Exercise: n = 15, 6 m/9f, mean age 69.4. Control: n = 15, 6 m/9f, mean age 68.5		KCCQ BDI 6MWT Diastolic Function
			NYHA class II/III		BNP
Kitzmann (2013)	USA	86 final testing	Total patients N = 63	4 months (16 weeks of continuous exercise training. 3 sessions per week, 60 min at 40%–70% HRR	LVEF
		88 exercise training	Exercise: n = 24, 23 m/9f, mean age 70. Control: n = 30, 25 m/6f, mean age 70		Peak VO_2 V_E/VCO_2 Heart rate 6MWT Diastolic Function
			NYHA class II/III		EDV & ESV SBP & DBP MLHF SF36
Palau (2013)	Australia	100	Total patients N = 26	12 weeks of interval exercise training. 2 sessions per week, 20 min. Subjects started breathing at a resistance equal to 25–30% MIP for 1 week and each subsequent session was adjusted to 25–30% MIP	LVEF
			Exercise: n = 14, 7 m/7f, mean age 68. Control: n = 12, 6 m/6f, mean age 74		Peak VO_2 V_E/VCO_2 Heart rate 6MWT Diastolic Function NT-proBNP
			NYHA class II/III/IV		MLHF
Smart (2012)	Australia	87.6	Total patients N = 25	16 weeks of interval exercise training. 3 sessions per week, 30 min at 60–70% peak VO_2	LVEF
			Exercise: n = 12, 7 m/5f, mean age 67. Control: n = 13, 6 m/7f, mean age 61		Peak VO_2 V_E/VCO_2 Heart rate Diastolic Function
			NYHA class I/II		MLHF

0.85 ml.kg^{-1}.min^{-1}(95% CI.0.05 to 1.65, p = 0.04); diastolic function; E/A ratio MD 0.07(95% CI 0.02 to 0.12, p = 0.005); E/E′ ratio MD -2.31(95%CI-3.44 to −1.19, P < 0.0001); Deceleration time(D_T)MD −13.2 ms (95%CI -19.8 TO -6.5, P = 0.0001). This is the first meta-analysis to identify that exercise training may significantly improve this aspect of diastolic function. Three measures of diastolic function have shown a trend towards normalization after exercise training, and improved diastolic function due to exercise training has been previously demonstrated in health people [86], while previous work in HFpEF has failed to show a trend towards improved E/A and D_T in people with HfpEF [70]. So further well designed studies of HFpEF are required to provide the more accurate information about exercise effect on diastolic function of HFpEF. Both meta-analysis report safety that no death was directly attributable to exercise.

2.3 For End-Stage Heart Failure

Heart transplant(HTx) and left ventricular assist devices(LVADs) are known to be the gold standard treatment method for patients with end-stage heart failure. But previous studies shown the exercise capacity and quality of life(QOL) are poor in patients with HF, HTx and LVAD [3–6].The exercise capacity in HTx patients is as low as 50–60% that of healthy groups due to prolonged deconditioning, muscle vesting, and a denervated heart [87]. Exercise capacity in patients with LVAD are lower when compared with the HTx patients may be due to the long waiting period for HTx associated with deterioration of functional status [88]. Meta-analysis of HTx patients [89] showed that exercise training(ET) could improve HTx patients exercise capacity and QOL. There also 4 studies proved the exercise efficacy on the capacity of LAVD patients [88, 90–92]. One recent study investigated the effect of exercise training in patients with end-stage failure, HTx patients and LVAD patients respectively on maximal consumption test(Pvo_2), Beck Depression Inventory(BDI) and State Trait Anxiety Inventory(STAI), Short Form 36(SF-36), and pulmonary function tests(PFTs). All the patients were given a supervised cardiac rehabilitation program, consisting of 90-min sessions, 3 times a week, for 8 weeks accompanied by a physiotherapist at the hospital. The program included flexibility exercise(range of motion, stretching exercises),aerobic exercises[60–70% maximal oxygen consumption test(p VO_2),ratings of perceived exertion 12–14,30 mn/session],strengthening exercises(250–500 g, upper/lower extremities, 8 muscles),breathing exercises, and relaxation exercises. The results showed that significant improvement was observed in all forced vital capacity(%),forced expiratory volume in 1 second(%), Pvo2,BDI and most of the subscores of the SF36 scores at the end of the exercise, compared with the pre-exercise period(p < 0.05) [93]. Andrew N et al. conducted a retrosptective study about exercise rehabilitation in 201 patients who underwent heart transplant(HTx) at Mayo Clinic between June 1, 2000, and July 31, 2013. They stated that Number of CR sessions attended in the

first 90 days after HTx predicted survival when controlling for baseline post-HTx 6-min walk test(6 MWT)results and rejection episodes. This study demonstrated for the first time an association between CR and long-term survival in patients with HTx [94]. Further work should clarify the most beneficial aspects of CR for patients with HTx, LVAD.

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Chapter 4
The Benefits of Exercise Training on Aerobic Capacity in Patients with Heart Failure and Preserved Ejection Fraction

Danilo Marcelo Leite do Prado and Enéas Antônio Rocco

Abstract Heart failure with preserved ejection fraction (HFpEF) is defined as an inability of the ventricles to optimally accept blood from atria with blunted end-diastolic volume response by limiting the stroke volume and cardiac output. The HEpEF prevalence is higher in elderly and women and may be associated to hypertension, diabetes mellitus and atrial fibrillation. Severe exercise intolerance, manifested by dyspnea and fatigue during physical effort is the important chronic symptom in HFpEF patients, in which is the major determinant of their reduced quality of life. In this sense, several studies demonstrated reduced aerobic capacity in terms of lower peak oxygen consumption (peak VO_2) in patients with HFpEF. In addition, the lower aerobic capacity observed in HFpEF may be due to impaired both convective and diffusive O_2 transport (i.e. reduced cardiac output and arterio-venous oxygen difference, respectively).

Exercise training program can help restore physiological function in order to increase aerobic capacity and improve the quality of life in HFpEF patients. Therefore, the primary purpose of this chapter was to clarify the physiological mechanisms associated with reduced aerobic capacity in HFpEF patients. Secondly, special focus was devoted to show how aerobic exercise training can improve aerobic capacity and quality of life in HFpEF patients.

Keywords Exercise • Aerobic capacity • Heart Failure with Preserved Ejection Fraction

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1 Introduction

Heart failure with preserved ejection fraction (HFpEF) is defined as an inability of the ventricles to optimally accept blood from atria with blunted end- diastolic volume response by limiting the stroke volume and cardiac output [1]. The HFpEF prevalence is higher in elderly and women and may be associated to hypertension, diabetes mellitus and atrial fibrillation [2, 3]. It is also noted that patients with chronic heart failure with both normal and reduced sistolic function have similar mortality rates [3, 4].

The primary chronic symptom observed in HFpEF patients is severe exercise intolerance and consequently decreased quality of life. In this context, prior study demonstrated a reduced aerobic capacity in terms of lower peak oxygen consumption (peak VO_2) in HFpEF than age/gender- matched controls [5]. In fact, the lower aerobic capacity observed in HFpEF may be due to impaired both convective and diffusive O_2 transport (i.e. reduced cardiac output and arteriovenous oxygen difference, respectively). In addition, scientific evidences [5] suggest that peripheral "non cardiac" factors are important contributors to exercise intolerance in HFpEF patients. Within this context, potential peripheral mechanisms that may reduced exercise tolerance in HFpEF are associated to skeletal muscle atrophy and reduced type I (oxidative) muscle fibers [5].

Aerobic exercise training has been recommended as non- pharmacological treatment for patients with a range of different comorbidities [6–8]. In this regard, exercise training program can help restore physiological function in order to increase aerobic capacity and improve the quality of life in heart failure patients (Table 4.1 and Fig. 4.1).

Thus, the primary purpose of this chapter was to clarify the physiological mechanisms associated with reduced aerobic capacity in HFpEF patients. Secondly, special focus was devoted to show how aerobic exercise training can improve aerobic capacity and quality of life in HFpEF patients (Table 4.2 and Fig. 4.2).

Table 4.1 Studies that evaluated aerobic capacity in HFpEF patients

Study	Sample	Peak VO_2 (ml/kg/min)
Dhakal et al. [9]	48	↓ 13.9 ± 0.5
Abudiab et al. [10]	109	↓ 9.8 ± 3.0
Bhella et al. [11]	11	↓ 13.7 ± 3.4
Borlaug et al. [12]	21	↓ 12.7 ± 3.1
Borlaug et al. [13]	17	↓ 9.0 ± 3.4

Abbreviations and symbols: ↓ = decrease when compared with healthy control

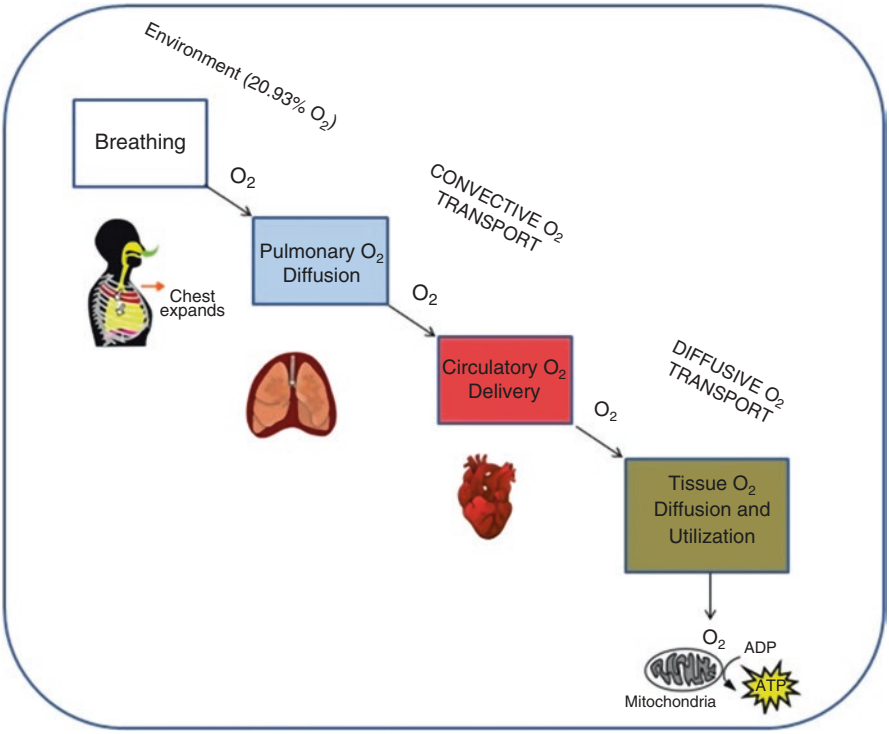

Fig. 4.1 Interaction between convective and diffusive components of O_2 transport during physical exercise

Table 4.2 Studies that evaluated the effects of exercise training in aerobic capacity and quality of life in HFpEF patients

Study	Exercise training	Duration	Peak VO_2 / quality of life
Smart et al. [14]	Endurance training (Duration = 30 min/ Intensity = 60–70% peak VO_2)	16 weeks (3 sessions per week)	↑
Kitzman et al. [15]	Endurance training (Duration = 15–20 min/ Intensity = 40–70% HRR)	16 weeks (3 sessions per week)	↑
Edelman et al. [16]	Endurance + resistance training endurance training (Duration = 20–40 min/ Intensity = 50–70% peak VO_2). Resistance training (volume- 15 repetitions per exercise/ Intensity = 60–65% 1 RM).	24 weeks (2–3 sessions per week)	↑

Abbreviations and symbols: ↑ = increase when compared with pre intervention; *HRR* = heart rate reserve; *RM* = repetition maximum

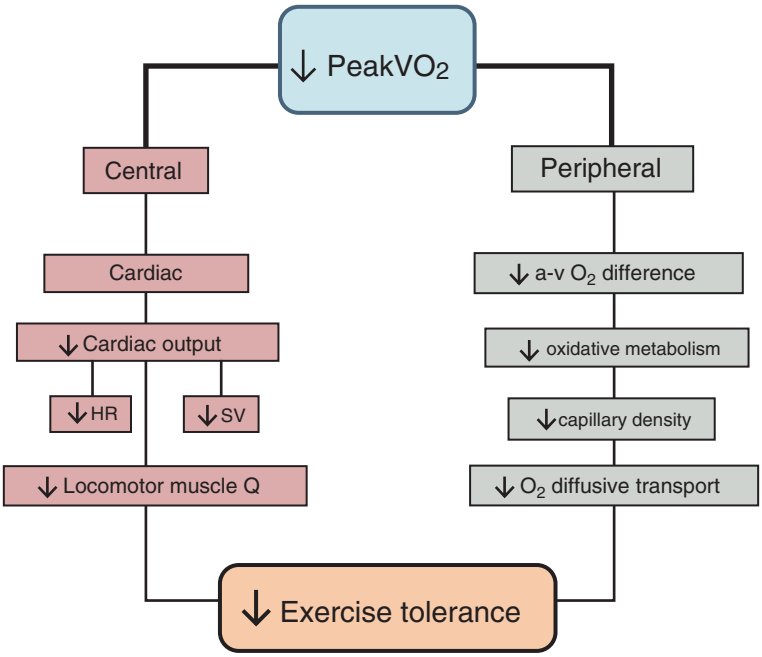

Fig. 4.2 Physiological mechanisms associated for the reduction of aerobic capacity in HFpEF patients
Abbreviations and symbols: *HR* = heart rate; *SV* = stroke volume; *Locomotor muscle Q* = locomotor muscle blood flow; ↓ = decrease

2 Aerobic Capacity in HFpEF Patients

There is a growing body of evidence indicating impaired aerobic capacity in HFpEF patients [9, 17, 18]. For instance, Kitzman et al. [18] showed a reduction in peak VO_2 in HFpEF patients compared with normal subjects (11.6 ± 4.0 versus 22.7 ± 6.1 ml/kg/min, respectively). Moreover, the authors demonstrated significant exercise intolerance in HFpEF patients as indicated by a lower peak workload than control subjects (407 ± 143 versus 705 ± 174 kpm/min, respectively) [18]. In the same way, Haykowsky et al. [17] observed lower aerobic capacity in HFpEF patients when compared to healthy age- matched controls (14.3 ± 0.5 vs. 20.4 ± 0.6 ml/kg/min, respectively) (Table 4.3 and Fig. 4.3).

Table 4.3 Effects of a 12- week aerobic exercise training program on cardiorespiratory measurements in a patient with HFpEF

	PRE	POST	Δ %
Exercise time, (min)	8.0	11.0	27.3
VO_2 VAT, (ml/kg/min)	13.3	19.2	31.0
$VEVCO_2$ slope, (units)	40.1	36.5	−9.0
$VEVO_2$ slope$_{, isotime}$ (units)	41.9	28.5	−32.0
$PetCO_2$ VAT, (mmHg)	31.1	37.5	17.0
(Δ $PeTCO_2$ rest-VAT)	1.0	5.0	80.0

VAT = ventilatory anaerobic threshold

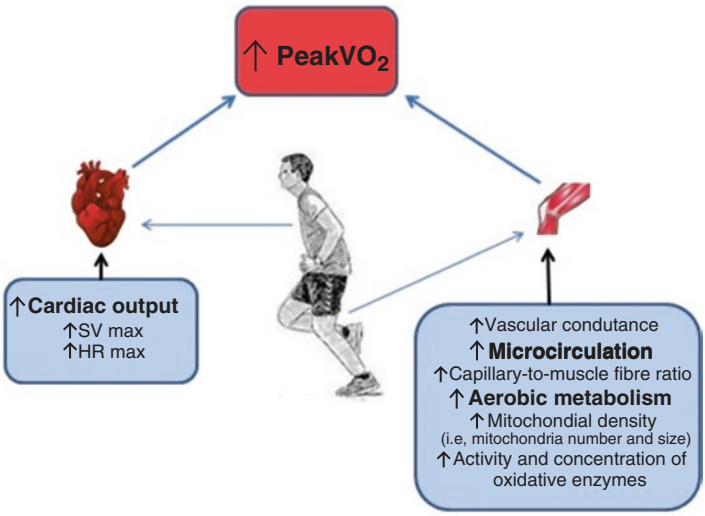

Fig. 4.3 Physiological mechanisms associated for the improvement of aerobic capacity in healthy subjects after aerobic exercise training
Abbreviations and symbols: *SV* = stroke volume; *HR* = heart rate; ↑ = increase

2.1 What Are the Physiological Mechanisms Related to Reduced Aerobic Capacity in HFpEF Patients?

In accordance with Fick principle, peak VO_2 is the product of cardiac output and arterial- venous oxygen content difference, on which is dependent the appropriate oxygen delivery to and/or oxygen extraction by the exercising skeletal muscles.

Peak VO_2 = CO X (a- VO_2 difference)
CO = cardiac output; a-VO_2 difference = arterial- venous oxygen difference.

Impairments in either convective O_2 transport (product of arterial O_2 content x blood flow) to the working locomotor muscles or diffusive O_2 transport from muscle

capillaries to mitochondria during physical exercise are the key determinants of reduced aerobic capacity in different comorbidities [5, 19, 20].

In this respect, a growing number of investigations have shown both cardiorespiratory and muscle metabolism abnormalities in HFpEF patients [5, 10, 17].

During physical exercise cardiac output (CO) is an important component on oxygen delivery to working muscle *(convective O_2 transport)*, in which is observed a close relationship between an increase in CO and VO_2. Within this context, most studies have reported that exercise VO_2 and CO are depressed in HFpEF [10, 12, 21]. For instance, compared to healthy subjects, HFpEF patients demonstrated a CO reserve limitation. Accordingly, previous investigation [10] observed that slope of the increase in CO relative to VO_2 was 20% lower in HFpEF patients compared with controls (5.9 ± 2.5 vs. 7.4 ± 2.6 L blood/ L O_2, respectively). *What are determinants of cardiac output limitation during physical exercise in HFpEF?* In fact, cross-sectional studies [12], suggest that both a blunted in stroke volume (SV) and heart rate (HR) response are associated. A lower SV observed in HFpEF patients are related to: (1) an impaired reduction in end- systolic volume by inadequate enhancement in contractility; (2) blunted afterload reduction and (3) diastolic dysfunction [10].

During physical exercise SV increases as result of an increase in end- diastolic volume by means of the *Frank- Starling mechanism* and as a result of increased left ventricular contractility (i.e., decrease in end-systolic volume). However, Kitzman et al. [18] demonstrated in HFpEF patients during cycle ergometer exercise an inability to augment SV by *Frank- Starling mechanism* in which is associated with a elevated diastolic pressure-volume ratio. In fact, these data suggest that reduced SV response during exercise are associated to abnormalities of diastolic function that limited left ventricular filling. Furthermore, Tan et al. [22] using speckle tracking echocardiography during submaximal exercise demonstrated both reduced myocardial systolic strain and rotation, lower left ventricular suction and delayed untwisting in patients with HFpEF. Based on these findings, the authors concluded that HFpEF patients have abnormalities of both systolic and diastolic function that become more apparent during physical exercise (Table 4.4 and Fig. 4.4).

With regard to vascular conductance, previous investigations [10, 13] have observed attenuated reduction in systemic vascular resistance during exercise in HFpEF patients. In fact, the impaired systemic vasodilation during exercise is known to reduce both cardiac ejection and muscle perfusion in patients with HFpEF. Importantly, the attenuated ability of skeletal muscle vasculature to dilate during physical exercise may be due to impaired peripheral arterial endothelial function.

Table 4.4 Recommendations for aerobic exercise prescription for HFpEF patients

Duration	Intensity	Weekly frequency
10–50 min	40–80% peak VO_2;	2–5
	40–70% HR reserve;	
	at VAT	

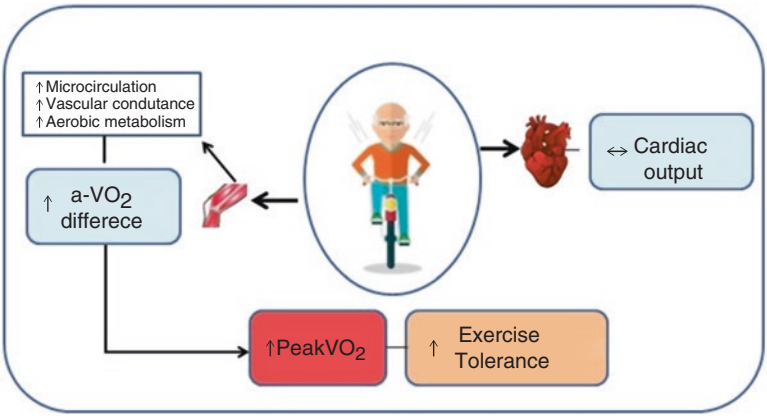

Fig. 4.4 Physiological mechanisms associated for the improvement of aerobic capacity in HFpEF patients after aerobic exercise training
Abbreviations and symbols: ↑ = increase; ↔ = unchanged

In respect to HR response during physical exercise, HFpEF have shown slower heart rate rise and lower peak heart rate than healthy match subjects [13]. This finding suggest a chronotropic incompetence associated to abnormal autonomic modulation during physical exercise in HFpEF patients.

Concerning the non cardiac 'peripheral' factors, it has been demonstrated an important role in limiting exercise tolerance as the reduced aerobic capacity in HFpEF patient [5]. For instance, two previous studies observed that systemic arterial- venous O_2 difference is abnormally low in HFpEF patients [11, 17]. Likewise, in a recent investigation Dhakal et al. [9] incorporating invasive haemodynamic monitoring showed in HFpEF patients that a reduced peripheral O_2 extraction was attributable to impaired diffusive O_2 transport and utilization. *What are determinants of peripheral O_2 extraction limitation during physical exercise in HFpEF?* Potential peripheral mechanisms that may limit exercise tolerance are: (1) decrease skeletal muscle mass; (2) alterations in skeletal muscle fiber type distribution (i.e, reduced type I oxidative muscle fibers) and (3) impaired blood flow to and/or extraction by the active skeletal muscles [9, 17].

Taken together, with the aforementioned findings it is reasonable to suggest that peripheral abnormalities may also be related with reduced aerobic capacity in HFpEF patients. Furthermore, aerobic capacity impairment observed in HFpEF patients may be associated with a reduced capacity to engage in both daily occupational activities and recreational tasks. Accordingly, becomes important the use of therapeutic interventions that improves aerobic capacity and therefore the quality of life in patients with heart failure.

3 The Effects of Exercise Training in HFpEF Patients

Adherence to a exercise training program results in physiological adaptations that characterize the specific adaptative responses. In this respect, previous investigations have shown that aerobic exercise training may increase peak VO_2 by between 10 and 20% when sedentary individuals are submitted to a specific period of aerobic exercise training [20].

Importantly, studies have shown an increase in aerobic capacity after exercise training program in patients with different cormorbidities such as cardiorespiratory diseases [7, 8, 14]. In this respect, there is a growing body of evidence indicating the improvement in aerobic capacity after exercise training in HFpEF patients [14, 16, 23]. It is important to point out, that an increase between 16 and 24.6% is observed after aerobic exercise training in HFpEF patients [14, 24]. Furthermore, after exercise training program the HFpEF patients demonstrated a significantly increase in exercise tolerance *(~63%)* as noted by 6- min walk test [24]. In a recent meta-analysis, Panday et al. [23] evaluated the effects of exercise training on aerobic capacity, quality of life and diastolic function in 276 patients with HFpEF. The authors observed two important findings: (1) exercise training increase both aerobic capacity and quality of life in patients with HFpEF and (2) exercise training in these patients is not associated with any significant change in resting diastolic or systolic function.

3.1 What Are the Physiological Mechanisms Underlie Increased Aerobic Capacity in HFpEF Patients After Aerobic Exercise Training?

Considering the physiological mechanisms responsible for increasing aerobic capacity after exercise training programs, these may be dependent on central (cardiac output) as well as peripheral components (a-VO_2 difference).

To date, little is known regarding the physiological determinants of the improvement in aerobic capacity in HFpEF patients. However, accumulating evidences [11, 25, 26] suggests that peripheral mechanisms are involved on increasing aerobic capacity after exercise training in patients with HFpEF.

This is supported by a study from Haykowky et al. [25] that demonstrated an increase in aerobic capacity after 4 months of exercise training program in elderly HFpEF patients, but nevertheless, this was not translate into a significant training related increase in peak cardiac output. Instead, an increase in peripheral O_2 extraction accounted for a substantial portion of the improvement in aerobic capacity after exercise training in HFpEF patients. In fact, this is not surprising due to this greater plasticity of peripheral mechanisms (i.e. locomotor skeletal muscle) on increase O_2 extraction from peripheral blood flow.

It is important to emphasize again that chronic heart failure induced impairments in both structural and functional components of the O_2 transport pathway, thus con-

tribute to reduced exercise tolerance and quality of life in these patients. Within this context, it is reasonable to suggest that aerobic exercise training may constrain or reverse these peripheral abnormalities by enhancing either skeletal muscle perfusion and oxidative metabolism [25].

4 Cardiovascular Rehabilitation: A Practical Approach

This practical example shows the effects of a 12- week aerobic exercise training program in a 65- year old male patient with heart failure (left ejection fraction: 45% and peak VO_2: 15.87 ml/kg/min). The symptoms presented by the patient before intervention were chronic fatigue and dyspnea on exertional.

The patient performed a maximal cardiorespiratory exercise test on a programmable treadmill before and after exercise training program. The exercise workload (speed and/or slope) was increased every 1 min with completion of the incremental part of the exercise test between 8 and 12 min.

The exercise training program consisted of three 60-min exercise sessions per week. Each exercise session included a 5- min warm-up, 40–50 min of continuous aerobic exercise on treadmill and 5 min of cool- down exercises. The aerobic exercise was performed with intensity at ventilatory anaerobic threshold (VAT) (Fig. 4.5).

At baseline, the patient demonstrated severe impairment in aerobic capacity as evidenced by peak VO_2 (15.87 ml/kg/min, 50% age predicted). Additionally, he demonstrated both lower ventilatory efficiency (VE/VCO_2 slope = 40.1 units) and abnormal $PeTCO_2$ pattern with small increment (Δ $PeTCO_2$ rest-VAT = 1 mmHg).

After 12- week aerobic exercise training program, the patient showed a significant increase in aerobic capacity.

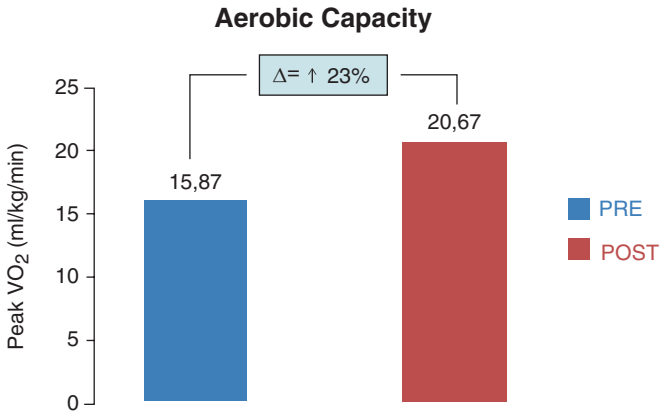

Fig. 4.5 The effects of a 12- week aerobic exercise training program on aerobic capacity in a patient with heart failure

In addition, the patient showed improvement in both exercise tolerance and ventilatory efficiency.

4.1 Comments

After 12- week aerobic exercise training the patient showed an increase in both aerobic capacity and ventilatory efficiency. Noticeable, after cardiovascular rehabilitation program the patient related an improvement of exertional dyspnea sense during performance of the tasks of daily living.

In fact, as can be seen in Fig. 4.6 (panel A), the patient demonstrated an important decrease in ventilatory demands during daily activities with different levels of energy expenditure expressed in METS.

In this context, during the activities of light intensity *(i.e. 2 METs – walking less than 2.0 mph)* was observed a decrease by around 27% of ventilatory demand.

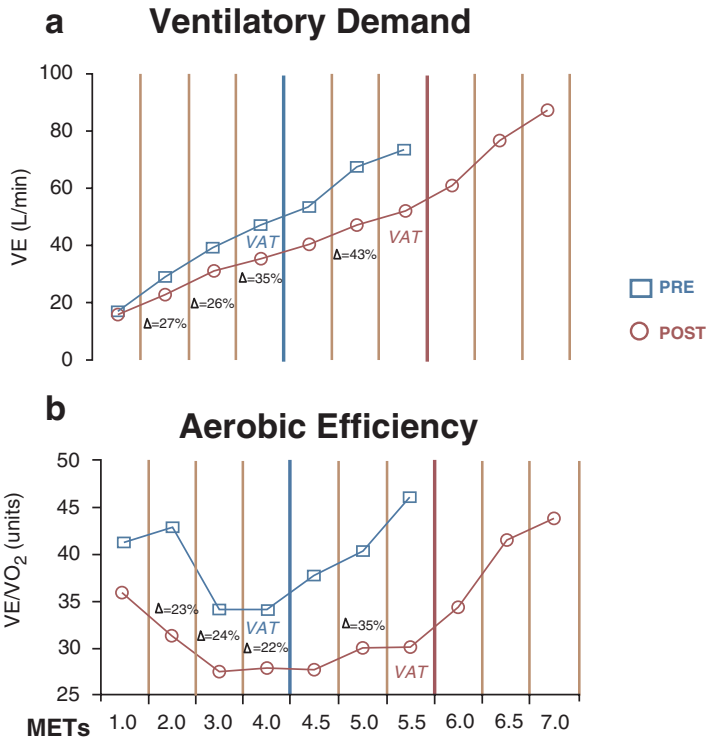

Fig. 4.6 The effects of a 12- week aerobic exercise training program on ventilatory demands (Panel **a**) and aerobic efficiency (Panel **b**) in a patient with ischemic heart failure
Abbreviations and symbols: *VE* = pulmonary ventilation; *VE/VO*$_2$ = ventilatory equivalent for oxygen

Moreover, for moderate-intensity activities *(i.e. 5 METs – walking at 3.5 mph)* the patient demonstrated a significant reduction by around 43% of ventilatory demand. It is also noted that after intervention he showed a reduction in ventilatory equivalent for oxygen at matched energy expenditure Fig. 4.6 (panel B). In fact, this finding reinforces a significant reduction in ventilatory demands for a given oxygen uptake.

Furthermore, after exercise training program was observed an improvement in muscle oxidative metabolism characterized by increase in VO_2 at ventilatory anaerobic threshold. Indeed, as can be seen in Fig. 4.6 (panel B) the patient showed a marked shift to the right of the VAT suggesting an increase in aerobic efficiency. Importantly, this finding reflects the patient capacity to perform tasks of daily living with less contribution of anaerobic metabolism.

On the basis of the above- mentioned findings, it seems reasonable to speculate that cardiovascular rehabilitation is of the utmost importance on improving quality of life in HFpEF patients. Within this context, Note et al. [27] evaluated the effects of exercise training on the quality of life in HFpEF patients through the short- form (SF-36). Specifically, after intervention the authors observed that 3 months exercise training performed in HFpEF patients positively affects general health perceptions and physical dimensions. Moreover, aspects related to both emotional status and social dimensions of quality of life also showed improvement after intervention.

5 Exercise Training Recommendations

The exercise training program for patients with HFpEF consist of aerobic exercise alone or combined with resistance training (concurrent training). It is also important to incorporate flexibility exercises before and after exercise session (Table 4.5).

5.1 Aerobic Exercise

Aerobic exercise training is typically performed at moderate-to high exercise intensities in a steady-state conditions of aerobic energy production, which allows the subjects to perform prolonged training sessions (i.e. up to 45–60 min). During aerobic training session is recommended to use large groups muscle (i.e, walking, cycling). Below follow the recommendations for aerobic exercise prescription.

5.2 Resistance Training

Resistance training is a form of physical activity that is designed to improve muscular strength and endurance by exercising a muscle or a muscle group against external resistance. Resistance training program has been utilised to target skeletal

Table 4.5 Recommendations for resistance training prescription for HFpEF patients

Sets/ repetitions	Intensity	Weekly frequency
1–2 / 8–15	40–60% 1- RM	2–3
	12–13 RPE	

RM = one repetition maximum; *RPE* = rating of perceived exertion
min = minutes; *HR* = heart rate; *VAT* = ventilatory anaerobic threshold

muscle dysfunction associated with chronic heart failure. In fact, the ability to perform necessary activities of daily living in CHF patients is related to muscle weakness.

5.3 Safety of Cardiovascular Rehabilitation Program

It is recommended that the exercise training program must be implemented in clinically stable HFpEF patient. In addition, the exercise program should be initiated in a supervised setting with direct supervision and monitoring. It should also be highlighted, before starting the cardiovascular rehabilitation, a maximal exercise test is recommended for evaluating cardiorespiratory responses during exercise.

Finally, no adverse events (deaths, hospitalizations, and cardiovascular events) were reported during exercise program in HFpEF patients [23].

6 Summary

Patients with HFpEF show poor exercise tolerance that is associated with reduced quality of life. Up to now, accumulating evidences shows that reduced peak VO_2 observed in HFpEF may be due to impaired both convective and diffusive O_2 transport (i.e. reduced cardiac output and arteriovenous oxygen difference, respectively). In this context, exercise training program can help restore physiological function in terms of increase aerobic capacity and improve both morbidity and mortality in heart failure patient. Taken together, previous findings suggest that exercise training program can be used as an alternative therapeutic tool for the improvement of symptoms and consequently the quality of life in HFpEF patients.

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Chapter 5
Hypertension and Exercise Training: Evidence from Clinical Studies

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Abstract Hypertension is a worldwide prevalent disease, mostly manifested as its primary ethiology, characterized by a chronic, multifactorial, asymptomatic, and usually incurable state. It is estimated that more than one billion of the world population is hypertensive. Also, hypertension is the main cause of the two most frequent causes of death worldwide: myocardial infarction and stroke. Due to the necessity of the cardiovascular system to manage chronically increased levels of blood pressure, hypertension causes severe alterations in multiple organs, as the heart, vessels, kidneys, eyes and brain, thus increasing the risk of health complications. The heart is the main target organ and suffers several adaptations to compensate the increased blood pressure levels; nevertheless, long-term adaptations without proper control are extremely harmful to cardiovascular health. On the other hand, hypertension is a modifiable risk factor and its adequate control is highly dependent on lifestyle. Pharmacological treatment is of great success when adherence is high. Several classes of antihypertensive drugs are prescribed and can effectively maintain blood pressure within acceptable levels. However, non-pharmacological methods, as diet and exercise training, can not only optimize the treatment but also prevent or postpone hypertension development as well as its complications, acting as important complements to the ideal control of elevated blood pressure, and bringing together benefits beyond blood pressure decrease, as a general health status improvement and increased quality of life. There is consistent evidence that regular exercise training promotes several benefits when properly prescribed and practised, acting as "medicine" for dozens of chronic diseases. The effects of exercise training in blood pressure levels and in its mechanisms of control are of clinical relevance and efficacy. This chapter will describe the classical and recent results on the beneficial

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effects of different modalities of exercise training in the cardiovascular system of human primary hypertension, focusing on the mechanisms influenced by exercise training which help to decrease blood pressure and improve the cardiovascular system.

Keywords Hypertension • Exercise training • Blood pressure • Cardiovascular system

1 Pathophysiology of Primary Hypertension

Essentially, arterial pressure is the result of the interaction between cardiac output and peripheral resistance, and its maintenance within ideal levels is pivotal to the organism, as it guarantees the adequate tissue perfusion in every situation. For this reason, short-term and long-term mechanisms take part in this dynamic process to regulate blood pressure levels in accordance with the hemodynamic demand.

Figure 5.1 depicts the main mechanisms related to blood pressure control. Hypertension is installed when there is an imbalance of these mechanisms, either increasing pro-hypertensive factors and/or reducing depressor factors [4]. It occurs in response to the interaction between internal (mostly non-modifiable) and external (mostly modifiable) elements which may favour this imbalance.

Due to the complexity and multisystem nature of blood pressure control, it is not possible to determine only one mechanism which is responsible for primary hypertension onset and maintenance. Renal mechanisms of blood pressure regulation proposed by Guyton decades ago are still updated [5, 6]. Not less important, cardiovascular autonomic dysfunction, characterized mainly by sympathetic overactivity, is a major player in the hypertensive disease [7]. More recently, it was reported that this autonomic dysfunction can intensify inflammatory responses, thus contributing to accelerate pathologic processes involved in cardiovascular disease, including hypertension [8]. Also important to mention, vascular abnormalities represented by endothelial dysfunction, enhanced oxidative stress, and vascular remodelling has gained support to be the cause rather than the consequence of hypertension [9]. These vascular abnormalities are amplified by the interactions with other altered mechanisms involved in blood pressure regulation.

As seen in Fig. 5.1, there are internal and external conditions which are well known as potential risk factors for hypertension development. Fortunately, external risk factors can be modified by lifestyle changes. In this sense, exercise training act as a powerful alternative to complement pharmacological and dietetic interventions in the treatment of hypertension by improving most of the mechanisms involved in blood pressure control, thus contributing to blood pressure decrease.

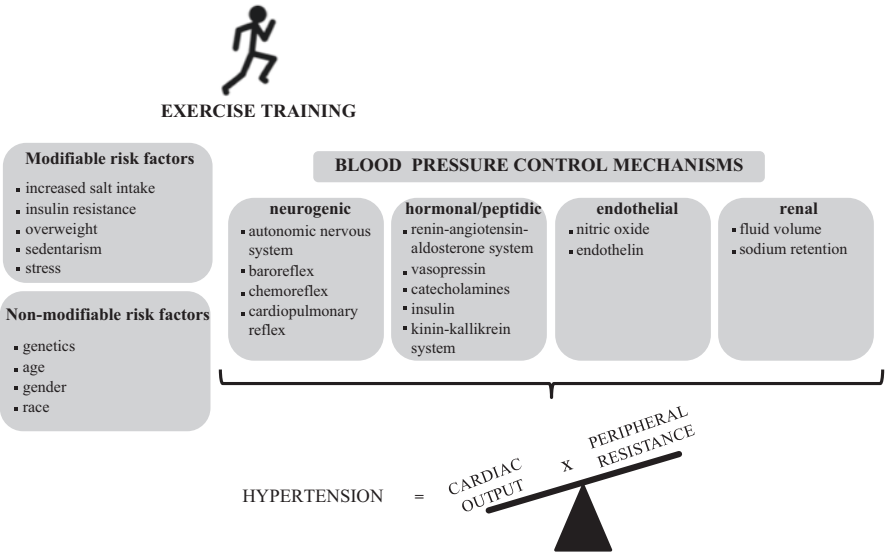

Fig. 5.1 Factors influencing mechanisms of blood pressure control: several mechanisms play to adjust cardiac output and vascular peripheral resistance to keep blood pressure within ideal levels. The presence of risk factors favours the imbalance of blood pressure control mechanisms, which determines the development of primary hypertension. Due to its multifactorial nature, it is not possible to identify which mechanism is responsible for primary hypertension establishment. Exercise training is able to modify some of the risk factors and by improving most of the mechanisms related to blood pressure control, can reduce blood pressure, and consequently reduce the cardiovascular risk in hypertensive individuals

The importance of blood pressure decrease in hypertension is not only to assure the adequate physiological status, but also to preserve the cardiovascular structure. The heart adjusts the cardiac output according to the metabolic demand. In face of high levels of blood pressure, the first attempt is to increase cardiac output in order to accommodate this hemodynamic overload; however, this augment works only in the acute phase and not when the stimulus persists. Therefore, the continuous hemodynamic overload triggers pathological hypertrophic and remodelling responses of the vascular (which explains the sustained increase vascular peripheral resistance in hypertension), and cardiac tissues. At first, these responses contribute to normalize cardiac performance; however, the complexity and progressiveness of cardiac hypertrophy classify this adaptation as a risk factor for hypertensive-associated disease/events, and as predictor of mortality [10]. At long term, pathological left ventricular hypertrophy (LVH) compromises cardiac function.

Decreasing left ventricular mass significantly contributes to the reduction of cardiovascular risk [11]. Once more, exercise training can be a good partner on it.

2 Anaerobic Exercise Training

Anaerobic exercise, by a biochemical concept, is an exercise in which the main source of energy for force and work production comes from energetic pathways that are not dependent of oxygen. Those exercises have a rapid duration, mainly because of the velocity of the work demand (which cannot be achieved by oxygen perfusion speed), but also demands lots of energy and produces force and work in elevated levels.

Classic examples of anaerobic exercises are the 100 m running, 50 m swimming, 100 m with hurdles, and the majority of short-term track and field sports at the Olympics. Nevertheless, even common movements in the daily life like seating, standing, jumping, squatting, putting an object in a shelf and all short-term life activities are also possible due to anaerobic energy production.

Another classic example of short-term exercises is the resistance training (RT), or strength training. By means of convention, the authors adopted the term RT as a synonym of the other examples in this chapter.

RT is one of the most used anaerobic exercise interventions in cardiac prevention and rehabilitation not only because of the energetic benefits *per se,* but also for other morphophysiological benefits in the skeletal muscle, bones, and the cardiovascular system [12, 13].

In hypertension, RT has been used as a resource for its treatment and comorbidities attenuation, reducing the peripheral vascular resistance, and thus, the systemic blood pressure [12, 14]. This reduction can be due to the elevated number of metabolites present in the skeletal muscle during and after the exercise session [15]. These metabolites like H^+, ADP, lactate, CO_2, among others, are vasodilators, and when in high concentrations, can elicit a powerful reduction in the local blood pressure [15].

An increasing number of studies have been showing the chronic beneficial effect of RT in the treatment of hypertension, with significant drops in both systolic and diastolic pressure, decreased sympathetic tone, reduced peripheral vascular resistance, and also decreased risk for other life-threatening cardiovascular events, as myocardial infarction and heart failure [16–20].

Historically, RT has been seldom prescribed as an alternative for hypertension treatment mainly due to the absence of data regarding real effects in the blood pressure, being neglected by the recommendation of aerobic exercises. However, a recent meta-analysis has shown that RT has a significant contribution in the process of blood pressure lowering, mainly by reductions in the diastolic blood pressure, which is representative of the peripheral vascular resistance [21]. Moreover, RT also contributes to net blood pressure changes, with reductions around −3.87 mmHg for systolic pressure and −3.6 mmHg for diastolic pressure [19]. Although small, those blood pressure reductions are related with decreased risk of developing several hypertension-associated diseases, as coronary heart disease (decrease of 5%) and stroke (decrease of 8%). In addition, a decrease in all-cause mortality by 4% is also observed [19, 22].

RT can elicit important changes in the regulation of general circulation, mainly by adaptations of the autonomic reflexes (i.e. baroreflex, metaboreflex, mechanoreflex, chemoreflex and etc.). Changes in the blood flow of the active muscle during RT alter the venous return, resulting in a higher amount of blood returning to the right atria, activating the heart stretch reflex, resulting in the activation of Frank-Starling mechanism, thus increasing cardiac output and blood pressure. Changes in baroreflex sensitivity caused by chronic RT have been widely reported in the last years [23–25].

During the RT, baroreflex is almost completely abolished by the overactivation of other local reflexes, such as metabo-, chemo- and mechanoreflexes [26]. Among those reflexes, the chemoreflex is known to cause the major contribution to the attenuation of baroreflex activity during exercise, mainly by its function of controlling the levels of metabolites in the circulation (O_2, CO_2, H^+, ADP etc.) [24, 26].

The rise in blood pressure during exercise driven by the chemoreflex coincide with the decreases in O_2 presence and accumulation of lactate and H^+ [26]. This chemoreflex response is also one of the main pathways for post-exercise hypotension, the fall in the blood pressure levels below the resting values after exercise [26].

Another interesting category of anaerobic exercise that has been extensively investigated is the isometric exercise. Isometric exercises consist in exercises where muscle length and joint angle does not change while the muscle maintain a resistance against gravity, like holding a dumbbell in front of the face for a certain amount of time. Surprisingly, this exercise has been showing incredible benefits in reducing blood pressure, with values around −10.9 mmHg of reduction for systolic and −6.9 for diastolic components [21].

A recent meta-analysis demonstrated that isometric exercise can be beneficial in blood pressure reduction only in male adults over 45 years of age, in a low-intensity training regimen, three times weekly at 30% of maximal voluntary contraction, for more than 8 weeks [27]. In this study, hypertensive individuals showed a decrease of 5.91 mmHg in mean arterial pressure.

Another recent study showed that one single bout of low-intensity handgrip exercise (4 series of 2-min sustained handgrip contractions at 30% of maximal voluntary contraction) significantly reduced systolic blood pressure, with a tendency to reduce diastolic pressure, in daily life activities of pre- and stage 1 hypertensive men [28].

Some limitations to recommend isometric exercises to hypertensive patients have to be addressed. Firstly, the hypotensive effects of isometric exercise have been mostly investigated acutely. Secondly, the hypotensive effects do not seem to be long lasting. Finally, the number of bouts and time of execution, as well as which modality of isometric contraction should be executed to produce hypotensive effects are not well defined.

Although isometric exercises have a great potential of adherence, due to its simplicity and efficiency, and can produce meaningful blood pressure reductions, further investigations should be made in order to safely include isometric exercise in the exercise training programmes of hypertensive individuals.

As cited before in this chapter, not only blood pressure decrease but also the protection of the cardiac organ is an endpoint for hypertension therapy. Regarding

LVH, there is no clinical evidence that any modality of RT is able to improve this parameter in hypertensive patients.

2.1 Recommendations for Resistance Training Prescription

As any intervention in the hypertensive patient, the exercise program should consider some safety issues as well. The most important and relevant ones will be addressed here.

Regarding hypertensive individuals, it is very important to avoid sudden increases in blood pressure, which can cause the rupture of pre-established aneurisms in cerebral blood vessels, causing haemorrhage that can lead to disability or death. Therefore, avoiding elevated workloads or excessive short intervals that creates elevated fatigue is strongly recommended for hypertensive patients when practising RT.

During exercise, blood pressure responds differently in each part of the movement. While the concentric phase is performed (when the muscle is being contracted), there is a significant rise in the blood pressure in comparison to the eccentric phase, and even with the resting phase [29]. This increase during contraction can be determined by the temporary obstruction of the active muscle blood flow, which causes a rise in the systemic blood pressure; thus, in hypertensive subjects, high workloads without proper adaptation in this phase is highly not recommended. Just for comparison purposes, during a one maximal repetition test (1 MRT), the rise in blood pressure can be 2–3 times higher than the regular 120/80 mmHg values, with the highest value ever recorded in the literature around 320/250 mmHg during a 1 MRT [30].

Also, during the RT, beginners tend to execute the exercise improperly. For the professional accompanying the hypertensive subject, it is necessary to understandthe possible errors that could lead to unnecessary rises in the blood pressure. One of the most common errors in the exercise execution is the Valsalva maneuver. This maneuver consists in the abrupt inspiration and its interruption, causing significant rises in the thoracic pressure.

The dangerous effects of this maneuver consist in the sudden increase in thoracic and systemic blood pressure consequently, which can cause rupture of aneurisms and increase the risk for cardiac events. Also, the reflex response to this enormous increase in blood pressure is also an enormous decrease in blood pressure, which can lead to oxygen absence in the brain, resulting in faint and dizziness [29, 31]. Therefore, during the execution of the RT, normal expiration flows should be maintained during the concentric phase, thus avoiding the risk of the Valsalva maneuver.

The architecture of the training program is also very important when applying the concepts for hypertensive individuals. During the RT, the control of the blood pressure is only possible via the aspects of the exercises. For this reason, it is crucial

to observe the following points when prescribing a RT for hypertensive individuals:

- High intensity exercises are known to cause higher increases in blood pressure than moderate exercises [32]. The control of the exercise intensity should be carefully considerate, with preference for the moderate-intensity regimen;
- Exercises with short intervals also lead to higher increases in blood pressure. Intervals between exercises should be long enough to reestablish blood pressure close to the beginning levels [33, 34];
- Exercises executed to voluntary exhaustion are not recommended, because they may cause significant increases in blood pressure [30, 32];
- Exercises that recruit great muscle groups or multiarticular exercises that recruit many muscles are also known to cause more enhanced increases in blood pressure than exercises recruiting small or less muscle groups [35].

These considerations should be taken into account mainly in the beginning of the training program. With the progression of the patient, more intense and diverse training regimens might be incorporated, for more sustained and significant benefits for the patient's health, always avoiding unnecessary risks.

3 Aerobic Exercise Training

Aerobic exercise is by definition an exercise in which the energy produced for its maintenance occurs in the presence of oxygen. These exercises are usually of long duration and generate great amounts of energy. Different from the anaerobic exercise, it takes longer to produce the same amount of energy.

The great advantage of aerobic energy production is the efficiency of the pathway, in which every substrate (proteins, carbohydrates and lipids) can be burned into ATP. Also, the aerobic energy production can adequately sustain a longer workload without greater interruptions.

The aerobic exercises are totally dependent of the cardiopulmonary system for exchange, transportation and removal of O_2 and CO_2, thus, this same system is the main benefited from the stress and overload caused by aerobic exercises.

Aerobic exercise has been the main exercise alternative for the treatment of hypertension due to its benefits in heart, vessels, lungs, muscles and all systems involved in the regulation of blood pressure [12, 23]. The benefits of aerobic exercises to its practitioners begins with increased cardiac output, non-pathological left ventricular hypertrophy, better vascular compliance, diminished peripheral vascular resistance, increased muscle oxidative capacity, among others [14, 36].

For the hypertensive patient, aerobic exercises, either performed acutely or chronically, can positively affect the vessels, by increasing compliance (i.e. as the capacity of the vessel to contract and relax, mainly relax); the heart, by increasing the pumping capacity, reducing heart rate and the coronary flow pressure; the muscles, that act as a powerful venous return pump; the peripheral flow, by diminishing

the peripheral resistance and thus the systemic pressure; the autonomic nervous system, by adjusting the sympathovagal balance, mainly by increasing vagal activity, which is beneficial for heart protection; and many other benefits [37].

As cited earlier in this section, the muscle metabolites produced during exercise have a robust contribution in the reduction of the local blood pressure. Interestingly, as opposite of the local muscular response (blood pressure reduction), systemically, the blood pressure is augmented, mainly driven by the increased sympathetic activity in the heart and the vessels. This phenomenon is called functional sympatholysis, in which the abolishment (the lysis) of the systemic sympathetic activation in a specific tissue happens by a local hypotensive factor, like metabolites and other vasodilators (nitric oxide in the active tissue) in the skeletal muscle during the exercise. This mechanism drives the blood flow to the active tissues which, due to the vasodilation, are more susceptible to blood perfusion and oxygen exchange, facilitating the energy delivery during exercise. This is one of the mechanisms explaining the drop of blood pressure after an acute aerobic exercise session, and also after chronic exercise programmes, altogether with increased vagal activity and reduced peripheral vascular resistance [38].

Additionally, exercise is known as a modulator of the baroreflex, as it was shown by Laterza et al. (2007) [39]. In his study, hypertensive patients who never received any pharmacological treatment joined a combined exercise program. Measurements of the baroreflex were made by muscle microneurography and blood pressure recordings simultaneously. The results showed a recovery of the baroreflex activity to normal levels, together with significant reduction in sympathetic activity, and in blood pressure, indicating a powerful restoration capacity of the exercise regarding autonomic function and modulation in hypertension. Years earlier, it was demonstrated that aerobic exercise training elicited a modest baroreflex sensitivity improvement in mild and borderline hypertensive patients [40, 41].

Besides the positive effects in neurogenic mechanisms of blood pressure control, aerobic exercise training also influences the vascular peripheral resistance. Vascular remodelling is one of the compensatory adaptations to chronic increased levels of blood pressure, and once more exercise training can positively affect it, acting in the reverse remodelling of the vessels. Hansen et al. (2010) [42] showed that hypertensive patients after 16 weeks of moderate aerobic training reduced blood pressure accompanied by an increase in muscle capillary-fiber ratio in association with increased expression of vascular endothelial growing factor.

Aerobic exercise causes physiological LVH, differently from the pathological LVH caused by the increased overload. Changes in chamber size, wall thickness, inter-septum thickness and myocyte size are remarkable in the exercising heart. In hypertensive patients, it was observed that exercise training was associated with a paradoxical regression of LVH or even a prevention of cardiac hypertrophy [43]. A study conducted by Rinder et al. (2004) [44] aimed to compare the blood pressure-lowering capacity and reversion of the pathological LVH in hypertensive adults taking thiazides and exercise training. Although exercise showed a more reduced capacity of lowering blood pressure than thiazide, it reverted the pathological LVH as much as the pharmacological treatment. Moreover, other favourable effects as

increased aerobic and movement capacity, and decreased insulin resistance were achieved only with exercise training.

Another interesting study regarding cardiac structure and function after exercise training in hypertensive should be mentioned. Andersen et al. (2014) [45] reported that men with mild-to-moderate hypertension, evaluated by echocardiography, importantly improved diastolic function after 3 months of football training in comparison with sedentary patients. After 6 months of the same training, parameters of cardiac structure were not changed, which means that, at least, cardiac hypertrophy was not in progress.

In elderly hypertensive patients, aerobic exercise training induced partial regression of LVH [46]. Positive repercussions of exercise training in cardiac function of old hypertensive subjects were also reported [47]. On the contrary, despite the reduction in blood pressure, and increased physical and strength capacities, Guirado et al. (2012) [48] showed that a 6-month of combined exercise training (aerobic + resistance) 3 times/week in controlled hypertensive elderly patients did not change parameters of morphology and function by echocardiography.

Mechanisms behind exercise-induced changes in cardiac structure and function are vastly studied in animal models, eliciting pathways of molecular and cellular levels; however, in humans, these mechanisms are not fully studied. Even though it is complicated to determine the influence of hypertension, exercise and pharmacological treatment to LVH and total heart function, exercise can be a strong contributor to the cardiac health improvement for the hypertensive patient.

3.1 Recommendations for Aerobic Exercise

As the majority of studies were conducted with aerobic exercise training for decades, it is the main recommendation for the alternative or adjuvant treatment for hypertension, with a "A" level of evidence and "I" class of recommendation, according to the American Heart Association [49]. Many studies have shown the potential benefits of aerobic exercise, with reductions around −3.5 mmHg for systolic and diastolic -3 mmHg [21].

Also, aerobic exercise is an excellent adjuvant treatment for hypertension due to its safety. Aerobic exercises consist in walking, running, biking, swimming, dancing, and other diverse activities that are usually very pleasant and can be executed for longer periods.

The aerobic exercise should be prescribed based on various methods, such as maximal heart rate (HRmax), percentual of reserve heart rate (%HRR), scales of perceived exertion (such as the Borg scale), subjective analysis of the expiration flow (if the subject could not talk while exercising, it is on the adequate intensity) or, by direct measurements (VO_{2max}).

According to the ACSM's recommendation for exercise prescription for adults, aerobic exercise should be practised for periods between 30–60 min of moderate to vigorous intensity, 3–5 times a week [36]. This recommendation is also corroborated by the American Heart Association for the treatment of hypertension [49].

Due to its cardiovascular necessity and greater muscle recruitment, the aerobic exercise has been demonstrated as the most significant tool for lowering blood pressure, also with more substantial decreases in blood pressure and more prominent benefits in the cardiac system than RT [21, 49].

In addition, the aerobic exercise does not affect only the cardiovascular system, it also changes other risk factors for the development and maintenance of elevated blood pressure, as reducing obesity and adipose tissue [50], reducing circulating LDL levels and increasing HDL levels [51], and controlling diabetes [52].

4 Other Modalities of Exercise Training

Although aerobic training complemented by resistance exercises is the current recommendation for hypertensive individuals to benefit from exercise adaptations, there are other modalities of exercise that can compose the training programmes for hypertension prevention and treatment. These modalities also present improvements in blood pressure profile, and contribute to the general benefits profited by exercise trainings.

In general, exercises that promote relaxing and control of respiration, as most of the modalities mentioned in the upcoming sections, are able to decrease blood pressure due to optimized cardiovascular reflex responses and improved modulation of the autonomic nervous system, mostly by decreasing sympathetic overactivity and increasing the vagal component.

It is important to mention that, although there is no high level of evidence and recommendation of the following modalities in terms of blood pressure decrease in hypertension, all of them can be practised by hypertensive patients under the specific recommendations and avoidances already presented in this chapter as a complement to aerobic training and healthy lifestyle.

4.1 Respiratory Training

Although involuntary and most of the time unnoticed, breathing is an important element of the cardiovascular homeostasis. Characterized by the diaphragm movements, the breathing pattern can be practised and optimized by respiratory trainings. Slow and regular breathing has been associated with blood pressure reductions in hypertensive patients.

A music-guided training to induce a slower and regular breathing pattern was tested in controlled and uncontrolled hypertensive patients (10 min/day, for 8 weeks). The authors showed that this approach was able to decrease systolic and diastolic blood pressure (−16.8 and −11.5 mmHg, respectively) [53]. Another study involving controlled breathing also reported positive effects of this practise in blood pressure levels of hypertensive patients. An acute protocol of controlled breathing at

6 cycles/min compared with spontaneous breathing showed that slow breathing reduced blood pressure and improved baroreflex sensitivity [54].

As mentioned in the introduction of this section, autonomic and reflex mechanisms are the main responsible determinants of blood pressure decrease after the adoption of slower breathing patterns. Lung inflation increases when breathing cycles are diminished; this mechanical alteration stimulates pulmonary stretch receptors and evokes the Hering-Breuer reflex to avoid lung over-inflation. This serves as an input to the medulla, a key region for cardiopulmonary reflexes, where information generated by arterial baroreceptors is converged and integrated [55]. Therefore, as the reflex mechanism dictates, in face of an acute blood pressure augment and/or lung inflation, a vagal-mediated response is activated, with decreased cardiac chronotropic and inotropic activities, and decreased vascular peripheral resistance, inducing systemic vasodilation, and consequently reducing blood pressure. As breathing cycles are continuously performed in lifetime, this mechanism is constantly activated, thus contributing to keep blood pressure in lower levels also in chronic evaluations.

Inspiratory muscle training (IMT) is a modality of respiratory training in which patients breathe against a load calculated from their maximal static inspiratory pressure [56]. Hypertensive patients who underwent IMT for 8 weeks at 30% of their maximal static inspiratory pressure presented decreased levels of daytime systolic and diastolic blood pressure (−7.9 and −5.5 mmHg, respectively) accompanied by a decrease in sympathetic modulation and an increase in parasympathetic modulation [56]. Using a similar IMT protocol, Ferreira et al. (2016) [57] demonstrated that, similarly to aerobic training, IMT reduced sympathetic activity and improved endothelial function in controlled hypertensive patients after 12 weeks of training.

4.2 Tai chi

Another example of exercise modality that favours slow and regular breathing training is tai chi, a low impact exercise which is commonly practised in China but has practitioners worldwide.

A systematic review concluded that tai chi is effective in lowering blood pressure in different populations [58]. Lo et al. [59] corroborated this result reporting decreases of 9.71 mmHg in systolic pressure and 1.96 in diastolic pressure, and improvements in exercise behaviour in hypertensive tai chi practitioners after 8 weeks. Pan et al. [60] also found significant reductions in the blood pressure of hypertensive patients and suggested that this reduction may be correlated with increased plasma levels of vasodilatory endogenous gaseous signalling molecules (NO, CO and H_2S).

4.3 Yoga

This modality is based on isometric, stretching and breathing exercises, deep relaxation techniques and meditation. All of these elements can be beneficial to hypertensive individuals, including isometric exercises, as discussed earlier in this chapter. A systematic review of randomized trials indicated that yoga is able to decrease blood pressure in hypertension, with a more significant decrease in systolic than in diastolic pressure and increased effectiveness in pre-hypertensive patients [61]. Another study using a sphygmomanometer before and after the yoga session encountered reductions of 12.4 mmHg and 8.6 mmHg in systolic and diastolic blood pressures, respectively, after 3 months of twice-a-week integrative yoga training in hypertension [62]. Although it may be an interesting alternative and complementary approach to hypertension exercise therapy, the real effectiveness of yoga in blood pressure levels is still inconclusive [61].

4.4 Pilates

Pilates training is a modality widely practised by people of all ages. It consists predominantly of posture and abdominal exercises which realign and strengthen muscles. The huge variance of exercises and possibility of adaptations enables to work from low to advanced levels. It is predominantly a dynamic resistance exercise, includes isometric elements and, most of the times, controlled breathing. Usually, pilates training integrates most of osteomuscular rehabilitation programs, although it can also take part in high performance training programmes.

Controlled trials regarding pilates training and the cardiovascular system very are scarce. Due to its combined nature, possible results of pilates in hypertension, having blood pressure decrease as the endpoint, may follow the resistance training understandings regarding the responsible mechanisms [63]; nevertheless, there is no consensus about blood pressure decrease with pilates training. An elegant study of Martins-Meneses et al. [64] with controlled hypertensive menopausal women showed significant decreases of both clinical and ambulatory blood pressure after 16 weeks of mat pilates.

5 Exercise Training and Pharmacological Interactions in Hypertension

Exercise has rose as a very promising non-pharmacological tool for the treatment of hypertension, mainly via decreases in heart rate, sympathetic activity and peripheral vascular resistance (PVR), as reported earlier in this section. However, pharmacological treatment is almost always necessary for the adequate control of

hypertension. In this context, exercise acts as an adjuvant, where the patient is exposed both to the medications and to the exercise routine.

Thus, it is important to understand the interactions between the effects of the medications and the body's physiological response to exercise in order to adequate exercise prescription and recommendations. In this section the most popular classes of antihypertensive drugs will be briefly described followed by the main interactions with exercise training. Important to mention is the fact that both medicated and non-medicated hypertensive patients can benefit from exercise training effects.

5.1 Diuretics

The diuretics are a class of medications aimed to reduce the total blood volume, extruding Na^{2+} and water from the extracellular matrix to the renal circulation, thus stimulating diuresis and decreasing blood volume, and consequently, the blood pressure. This mechanism is usually an initial effort to control the blood pressure, and the results are usually seen in the first weeks of usage [65, 66].

Some side-effects are the excessive extrusion of important ions like Na^{2+} and K^{+}, sometimes causing hypokalaemia and insulin resistance. The most used class of diuretics is the tiazidic (hydrochlorotiazide and dihydrochlorotiazide) accompanied by a hyposodic diet.

During exercise and treatment with diuretics, two aspects must be focused: (a) the hydration status of the patient and; (b) the level of K^{+}. Diuretics cause water loss and may be prejudicial for the exercise performance, causing dizziness and faint; therefore, adequate water ingestion is recommended.

Hypokalaemia is a common episode in the diuretic treatment of hypertension, seen by the loss of liquids caused by the tiazidic medications. In addition to this, the exercise causes rise in body temperature and increased sweating, which also increases rates of K^{+} loss via sweating. In a patient already losing K^{+}, is really important the screening of K^{+} levels to assure safety while in an exercise program for hypertension. Hypokalaemia can cause dizziness, faint and rhabdomyolysis, thus is very important a nutritional support for K^{+} alongside the exercise and the treatment with diuretics [66].

5.2 Angiotensin-Converting Enzyme Inhibitors (ACEi)

This class of anti-hypertensives act in a different setting of the blood pressure control, inhibiting the conversion of Angiotensin 1 in Angiotensin 2. The renin converts the angiotensinogen into angiotensin 1, and the Angiotensin-converting enzyme (ACE) converts the angiotensin 1 into angiotensin 2. The angiotensin 1 has a moderate to low capacity for blood pressure increases, but, its conversion by the ACE into

angiotensin 2 increases strongly its ability to increase blood pressure, by augmenting vascular constriction, resulting in increased PVR and heart rate [67].

As a target to pharmacological reduction of blood pressure, the ACEi were developed to stop the conversion of angiotensin 1 into angiotensin 2, reverting its hypertensive effects. The most common ACEi are the commercial versions of captopril and enalapril.

To this date, no significant interaction or problem has been reported in the literature regarding the use of ACEi and exercise. Recent studies have demonstrated that long-term use of ACEi prevents the reduction of muscle oxidative activity, which may be beneficial for older adults, prolonging the exercise capacity [68].

5.3 Angiotensin Receptor 1 (AT_1) Blockers

Another way of preventing the activity of the renin-angiotensin-aldosterone system in not only the inhibition of the enzymes, like the ACE, but also aiming the receptor blockade, as in the case of the blockade of the AT_1 receptors. This receptor is present in the cardiomyocytes, in the vessels and in the kidney, increasing heart rate, constriction and stimulating Na^{2+} retention, all to increase blood pressure. The blockade of this receptors stop the hypertensive effects of angiotensin 2, resulting in significant reductions in systemic blood pressure [69]. The most used AT_1 blockers are the commercial version of losartan and valsartan.

To this date, no interaction between exercise and use of AT_1 blockers were reported in the literature. In an experimental rat model, Leite et al. [70] found an increased metabolic expenditure in the animals treated with AT_1 blockers; however, these findings were not found in human trials.

5.4 Central Alpha 2 Agonists

This kind of anti-hypertensives were developed focusing on the alpha 2 adrenergic receptors present in the central nervous system, thus reducing the sympathetic activity, and consequently, the heart rate and blood pressure [71].

Those medications act as sympathomimetic, meaning that they act like the adrenergic neurotransmitter noradrenaline in the alpha 2 adrenergic receptors, inhibiting adenylate cyclase activity and prompting brainstem signals for vasodilation. The most used alpha 2 agonists are the commercial versions of clonidine, methyldopa and guanfacine.

The relationship between exercise and alpha 2 agonists are scarce in the literature. Due to the reduction in total sympathetic activity, delays in heart rate increase and blood pressure can be present in some cases, which may be seen with caution. Exercise can benefit the user of clonidine by increasing the alpha 2 receptor sensitivity.

5.5 Vasodilators

The vasodilators act directly in the vascular smooth muscle cells and are especially used in the emergency treatment of high blood pressure. Such action initiates relaxation of the vessels, decreasing peripheral vascular resistance and, consequently, blood pressure and afterload. However, these medications have a short and not-sustained effect, seen that the system rapidly resets to its hypertensive setting. The use of vasodilators is known to cause reflex tachycardia, because of the reduction of afterload, thus activating chambers distension reflex. This reflex activation may cause angina pectoris and myocardial infarction in patients with coronary artery disease. They are usually combined with other medications, like beta-blockers or diuretics.

5.6 Calcium Channel Blockers

The calcium channel blockers are designed to specially block voltage-gated calcium channels, avoiding the inward flux of calcium to the cell. These receptors are spread in the cardiac muscle, but are especially present in the sinoatrial and atrioventricular nodes, regulating the rate of contraction by the depolarization of the nodes around them. The Ca^{2+} blockers interrupt the influx of calcium to the cell, especially the L-type Ca^{2+} channels, avoiding the calcium entering, thus reducing the cross bridge forming and contraction; this blockade reduces the cardiac output and thus the blood pressure systemically [72].

Currently, two types of Ca^{2+} blockers are available, the dyhidropyridinic and the non-dyhidropyridinic forms. The dyhidropyridinic are derived form a molecule called dyhidropyridin, which reduces PVR and consequently blood pressure. The non-dyhidropyridinic form of the Ca^{2+} blockers are based in a variety of other molecules, such as phenylalkylamine and benzothiazepine [67, 72].

The most used drugs to block voltage-gated calcium channels are the commercial versions of amlodipine, clevidipine (dyhidropyridinic), verapamil and diltiazem (non-dyhidropyridinic).

The use of exercise alongside the Ca^{2+} channel blockers are related with reduced heart rate for the same amount of exercise of a normal individual, due to the reduction of cardiac contractility and output. These reductions end up in a discrete reduction in maximal oxygen consumption (VO_{2max}) [73]. These changes must be taken in consideration for the exercise prescription.

5.7 *Beta-Blockers*

Beta-blockers are pharmacological molecules designed to act and interrupt the binding site of the adrenergic agonists noradrenaline and adrenaline, the beta adrenergic receptors ß$_1$ and ß$_2$. These receptors when activated by the adrenergic agonists, prompt mediate intracellular response via G-protein coupling, resulting in increased contractility of the myocyte. This increase in myocyte contractility results in increased heart rate, cardiac output and blood pressure [74]. The blockade of the ß-receptors interrupts the intracellular response, thus avoiding the increases in contractility, and consequently the increases in heart rate and blood pressure [65].

Currently, three types of ß-blockers exist in the market, the ß-selectives, which bind specifically the ß-adrenergic receptors ß$_1$ and ß$_2$ (atenolol); the non-selectives, binding every adrenergic receptor, irrespective of classification (propanolol); and the ones with vasodilator properties altogether with the chronotropic effects (carvedilol) [74].

Although, in the face of the adequate physiological rationale behind the ß-blockers, many side-effects have been reported during the treatment, such as bronchospasms, severe bradycardia, glucose tolerance, LDL increases, among others [75].

Due to the chronotropic effects of ß-blockers, exercise prescription and screening should be carefully analysed. Usually, the individual exercising under ß-blocker influence shows reduced heart rate for the same amount of exercise, affecting the exercise monitoring through the heart rate. For the prescription, the test should be taken under ß-blocker influence, as well as the exercise regimen, thus avoiding biases in the monitoring.

Also, seen that the cardiac output is reduced due to the reduction in contractility, the VO_{2max} is also affected by the use of ß-blocker; therefore, exercise prescription based on the VO_{2max} is not recommended, being preferred other methods based on the rate of perceived exertion or lactate threshold.

6 Conclusions

Exercise training is an optimal tool to treat and prevent hypertension and its associated diseases and dysfunctions. Once the exercise program is adequately prescribed and accompanied, patients can benefit not only from blood pressure decrease and better regulation, but also from improved quality of life and general health status.

The most well conducted, reproducible, and conclusive studies were done with aerobic exercise training. For this reason, by now, aerobic exercises at low-to-moderate intensities are the first choice to safely promote beneficial effects in hypertension and must be the most predominant modality in exercise training programmes.

Despite the growing number of studies with resistance and isometric trainings in hypertension, there are remaining controversies and factors to be elucidated. Therefore, resistance exercises should only complement the training programmes due to their specific effects in bones and muscles (which will also help in aerobic training performance). Finally, adding other modalities that contribute to patient's adherence to a healthier lifestyle is welcomed, always respecting the specialized recommendations.

Importantly, exercise training does not substitute pharmacological treatment, and medications should not be stopped once exercise training begins. The ideal control of hypertension should include adequate diet, exercise training, and pharmacological treatment, supervised by a multidisciplinary team.

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Chapter 6
Effects of Exercise on Arrhythmia (and Viceversa): Lesson from the Greek Mythology

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Abstract Exercise represents an important lifestyle factor in all human ages when felt in harmony with other psycho-physical and environmental variables that affect individual life (e. g. quality of interest, affections, environment, diet and food). Consequently, in addition to the training level, the amount, intensity and modality of exercise (ana–/aerobic, isometric/isotonic), need to be personalized, considering the underlying diseases, which may benefit from it or worsening.

Greek mythology gives us good examples of the exercise concept's evolution.

From Discus-thrower to Spear-carrier the idea of physical activity is more effectively expressed. The Myron Discobolus displays the enduring pattern of athletic energy translated into the dynamic force given by the exercise. In Doryphoros instead, the physical activity is oriented to the achievement of the required psycophysical harmony, who's the concept is aimed of being expressed by the sculpture.

As outlined below, even in the field of arrhythmia, scientific evidence as well as clinical experience, supports the same concept: physical activity may be important while safely managed and personalized.

Keywords Exercise • Arrhythmia • Sudden death

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1 Arrhythmia and Exercise: Can We Accept the Risk?

Heart rhythm abnormalities detectable through an electrocardiographic strep (ECG), are only the funnel neck through which potentially all cardiac diseases may reveal their presence. Conversely, they may represent the direct cause of catastrophic events such as severe arrhythmias and sudden death, leading a hyper-alarmist attitude both in the society and medical opinion.

Actually, arrhythmia represents one of the most common cardiac disturbance in the Western World, with a prevalence and incidence rising in the last decades and with new atrial fibrillation (AF) cases globally estimated per year close to five million [1, 2]. Growing bodies of scientific efforts are, therefore, aiming at developing new technologies and advanced therapies to manage arrhythmia while allowing patients to lead a sustainable and acceptable lifestyle [3].

Arrhythmias in fact, have great impact on daily life, causing a more sedentary behavior; moreover, sudden cardiac death (SCD), occurring particularly in young population during exercise, results in a general restrictive attitude of both the families and medical community to practice any kind of physical activity [4].

Nevertheless, an increasing risk in worsening the underlying cardiac disease and the general cardiovascular status, driven by physical inactivity, has been reported [3].

Furthermore, in the recent years, advances in our knowledge of basic mechanisms involved in the induction and maintenance of AF as well as almost any kind of arrhythmia, has evolved rapidly, with a progressive extension of catheter ablation technology to peripheral Centre. Moreover, emerging developments in genetics, imaging, and informatics also offer new opportunities for personalized care, including those lifestyle modifications, such as physical activity, which may help in preventing AF and arrhythmic events recurrence [5].

In this regard, early identification of congenital and acquired arrhythmia-linked at risk individuals, has started to allow a more permissive approach respect to the leisure and more competitive physical activity [6].

Conversely, concerning the physical activity potency to induce pathologic arrhythmia in healthy people, the exercise's intensity and duration, coupled with underlying genetic and non-genetic risk factors, sequentially or simultaneously, contribute to the U-shaped relationship between rhythm disturbances and exercise amount. This hypothesis is largely supported and accepted [7]. Consistently, in terms of AF risk, this dose-response curve reflects the clinical evidence that, while the two life-styles extremes (sedentary versus strong endurance exercise) represent both hazardous behaviors, a low-to moderate physical activity reduce the AF potential occurrence [8, 9].

2 Arrhythmias and Customized Exercise Indications

Patho-physiology and molecular basis of exercise-linked arrhythmia in healthy versus genetically predisposed subjects, have been recently extensively treated [7] and do not met the purpose of this chapter. Here, practical advises, derived by the direct

experience of different pediatric and adult electrophysiology's and stress test Labs will be given, aiming at encouraging a personalized approach, avoiding excessive permissive as well as restrictive bias respect to the physical activity prescription in at risk population.

As a tip of iceberg, factors underlying the arrhythmia's clinical phenotype are rarely etiologic (gene-based rhythm diseases) while more frequently they play a pathogenetic role in triggering and modulating the arrhythmogenic events.

Ranging from healthy heart to complex cardiac diseases, the clinical spectrum of arrhythmias may include paroxistic to permanent events triggered by genetic/local or environmental-linked factors, expressing their presence, or the underlying cardiac disease, through few ECG abnormalities, with or without clinical symptoms.

Some arrhythmias, particularly those affecting young people, recognize defined genetic basis. These include Long QT Syndromes (LQTSs), ion chanelopathies, characterized by ion channel dysfunction which, in the presence of adrenergic stress, can lead to polymorphic ventricular tachycardia (VT) resulting in failed QT shortening during peak exercise (LQTS type 1) or early exercise, (type 2) with subsequent QT prolongation in late recovery.

Another genetic-based arrhythmia, the Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) (linked to the ryanodine receptor, RyR2, and calsequestrin-2) shows an early appearance (first decade) of adrenergic-driven polymorphic bidirectional ventricular tachycardia VT, leading, if untreated, to syncopal events and cardiac arrest [10].

A heterogeneous group of genetic (voltage-gated sodium channel, SNC5A) as well as complex clinical phenotypes, are associated to the Brugada Syndrome (BrS). In contrast to LQTSs and CPTV, the arrhythmic events are vagal-dependent at most, occurring at rest or after exercise, with some minority during early recovery (the latter at risk of great arrhythmogenesis).

Considering that, independently from their ECG phenotype (tachycardia from atrium-ventricular pre-excitation type Kent pathway, type Mahaim pathway, concealed accessory, reciprocity junctional) almost all the congenital arrhythmias affecting pediatric patients, nicely heal with ablation of the arrhythmogenic substrate, the decision of dose and modality of physical activity essentially concerns, at most, the timing for ablation procedure [11].

In a recent interesting study [12], addressing the significance and prognosis of ventricular pre-excitation (VPE) in asymptomatic children, the evaluation of the risk of sudden death in 91 young asymptomatic affected athletes was performed by trans-esophageal electrophysiological study, at rest and during pharmacological stress, to set their sports eligibility after the risk assessment and/or ablative treatment. The Authors concluded that, an adequate risk assessmentand/or ablative treatment, allow most of the studied subjects to safely participate in competitive sports, underscoring the importance of risk layering to avoid an un-useful in not dangerous, fishing-mode restriction of individual psyco-physical equilibrium as a whole, as well as a correct life style.

Concerning congenital cardiomyopaties, Hypertrophic Cardiomyopathy, HCM, and Arrhythmogenic Right Ventricular Cardiomyopaties, ARVC), are historically linked to young sudden cardiac death (SCD) particularly in athlete's population,

allowing past guidelines to prohibit exercise at all. Carefully monitoring and stress tests evidenced a defined HCM population (1.7%) showing ventricular arrhythmia during exercise, while ARVC-affected patients experience endurance exercise-linked symptoms [13].

Before the extension of early diagnosis and therapy of these congenital, genetic-based and multifactorial rhythm disturbances, the strong sport restriction was also aimed to prevent adrenergic-triggered events. Indeed, even current Guidelines statements claiming these indications, are based on expert opinion at most, without addressing extensive prospective studies. Actually, once the clinical diagnosis and risk assessment have been performed, proper pharmacological therapy or implantable cardiac device (ICD) assessed and careful follow-up scheduled and updated, the risk of sport participation can be considered low [14].

Currently, a personalized therapeutic approach, allow these patients to participate to competitive sports, anyhow considering that the achievement of the wished performance do not justify the device implantation and eventually the frequent inappropriate shock. This point as well as the level of sport eventually allowed is actually an active question; ongoing NIH-funded prospective observational study, (Lifestyle and Exercise inHCM (LIVE-HCM), comparing outcomes among individuals with HCM who are exercising moderately or vigorously, to the sedentary is enrolling the interested people matching the required criteria (http://livehcm.org/).

Furthermore, personalizing exercise models and protocols are important, taking into account that isotonic, not isometric, exercise, inducing cavity dilation, could be favorable in defined group of patients, such as those with HCM with smaller LV cavities and tendency toward obstruction. Studies performed in animal models of HCM and in patients affected by the disease, show that moderate exercise may be not just tolerated but even beneficial in decreasing symptom burden [15–17]. These observations lead us to consider physical activity as a true therapeutic tool who's the indications, doses, side effects, contraindications need to be carefully taken into account, independently from the arrhythmia's origin. In this regard Budts et al. gives practical recommendations relating to physical activity for adolescents and adults with congenital heart disease, even those with arrhythmia, except for patients with congenital rhythm or conduction disorders and with isolated congenital coronary artery anomalies [18]. Similar advises are also renewed by Stout et al. [19].

The task force recommended more familiarity with the appropriate diagnostic tests, according to the 36th Bethesda Conference report [20].

3 Supraventricular Arrhythmias

Concerning supraventricular arrhythmias such as Atrial Tachycardia and Atrial fibrillation, a genetic link has been recognized. In a recent elegant study performed on about 19,000 European patients, Lubitz et al., using genome-wide data from an independent large-scale analysis to test AF genetic risk scores (GRS) for association

with new-onset AF and stroke, have demonstrated that, while improving prediction minimally, GRS were associated with AF beyond established clinical risk factors. However, AF genetic risk was strongly associated with cardio-embolic stroke. Therefore, while particular attention must be paid to the genetic fingerprint, the polygenic nature of AF and the independent value of genetic information beyond clinical risk factors do not justify its inclusion into routine clinical decision-making, such as exercise indications [21]. In the general population, AF commonly affect individual over 50 years, with hypertension and structural heart disease representing two of the most frequent underlying substrate. Cardiovascular abnormalities are absent in up to 10% of patients with AF; risk associated factors in these patients include obstructive sleep apnea, obesity, and intense exercise. Nevertheless, clinical trials have consistently reported that moderate doses of physical activity might be of therapeutic value to AF already diagnosed patients, which is probably also linked to better control of classic risk factors for AF, including hypertension or diabetes mellitus [22].

Actually the link between AF and physical exercise has been extensively debated as above outlined with conflicting conclusions probably linked to the grouping of risk factors into the analysis (individual susceptibility, time, duration and exercise intensity and quality) [7]. Again, in a study published in 2016, a similar U-shaped relationship between physical activity levels and risk of AF in both men and women was identified; of note, exercise was protective against AF in two independent cohorts of middle aged postmenopausal and 60–70 aged women, the latter carrying cardiovascular risk factors [23–25].

The individual contribution to AF development directly elicited by time of starting, intensity and type of physical activity, need to be evaluated. It is unknown whether different modes of training (such as endurance and strength training) differ in their arrhythmogenic potential. It is know that endurance trained athletes with underlying cardiac disease have a higher risk of potentially fatal arrhythmia during sports activity. Furthermore, AF risk in athletes might be related to vagal tone, pressure/volume load atrial stretch, dilatation and fibrosis, alone or in combination.

In a recent study, performed in large cohort of about one million of adolescent males undergone to military obligatory service, Andersen et al. performed a cardiologic follow-up of about 26 years, to address the associations between exercise capacity and muscle strength with risk of vascular disease (ischemic heart disease, heart failure, stroke, and cardiovascular death) and risk of arrhythmia (atrial fibrillation or flutter, bradi-arrhythmia, supraventricular tachycardia, and ventricular arrhythmia or sudden cardiac death) [26]. By taking the advantage to use a very large population the Authors give a reliable indication on how high exercise capacity and muscle strength in late adolescence could be associated with areduced risk of subsequent vascular disease. Once again, exercise capacity seems to show a U shaped association with bradi-arrhythmia and with those rhythm disturbances driven by a direct association with risk of atrial fibrillation (Fig. 6.1a, b).

Fig. 6.1 (**a**) Myron'sDiscobolus, (British Museum, London, United Kingdom) (**b**) Doryphoros of Polykleitos (MuseoArcheologicoNazionale, Naples, Italy)

4 Current Suggestions and Concluding Remarks

Correct prophylaxis with aerobic training in aged population favoring a proper weight control, by keeping optimal heart rate around 70 beats per minute at rest; cardiorespiratory fitness, achieved through a personalized program of aerobic and resistance training, further extends AF freedom in these subjects, over and above the effect of weight loss [5].

By contrast, high endurance training, promoting heart chambers dilatation with fibrotic degeneration of cardiac myocytes, formation of reentry circuits and a marked bradycardia, are almost not advocated. Nevertheless, the pro-arrhythmogenic level of exercise, are not usually achieved by most of the AF patients. Consistently, recent data demonstrate an inverse relationship between physical activity and AF incidence in non-athlete cohorts [2, 27]. However, long term sustainment of these benefic effects, still need to be addressed. Also in our experience, in patients already suffering from persistent form of arrhythmia (including those with limited clinical features, such as mild tachycardia or ectopic beats), physical activity must be tailored to maintain adequate right heart rate trends.

As a general rule, arrhythmias affecting aged people recognize an ischemic origin at most, while those occurring in child and young population more often are related to a genetic or congenital background.

Overall, the most common congenital or inherited heart conditions associated with sudden death during sports include hypertrophic cardiomyopathy, coronary artery abnormalities, Marfan syndrome, and aortic valve disease. An increased risk is also associated with less common lesions such as complex defects (repaired transposition and single ventricle), and pulmonary vascular disease. Furthermore, certain forms of congenital long QT syndrome may be also at risk of arrhythmias-linked SCD during exercise. As adolescents and young adults undergo to progressively more demanding activities, comprehensive evaluation and counseling are essential. Tailored and personalized programs, based on scientifically defined and shared clinical protocols, may allow physical activity to contribute in the reduction of the overall risk of arrhythmias and/or the occurrence of arrhythmogenic events/triggering factors (e.g. the lowering of sympathetic trigger through shift of the neuro-vegetative system toward the vagal tone).

While risk factors for coronary heart disease or LV dysfunction usually are not typical in youth, in general physical activity in these situations is allowed only by respecting the required guidelines (see above), after a clinical consensus extended to all the medical area involved in the specific disease.

Concerning those patients holding ICDs, physical activity is obviously allowed and the devices set on the basis of expected effort.

Besides universally accepted management protocols for personalized exercise prescription in arrhythmia's affected patients are available [19], extensive basic and clinical prospective, controlled studies still need in this field. The risk otherwise, is to entrust exclusively to the common sense rather than to the protocols, the choice and amount of exercise to be prescribed to a defined patient.

In the Precision Medicine era [28], basic research may wish to allow the required quality of exercise to fit with the molecular mechanisms underlying the specific disease, while new rigorous large scale controlled studies will reduce the random medical therapeutic choices and increase the compliance of patients.

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Chapter 7
Exercise and Congenital Heart Disease

Junnan Wang and Bin Liu

Abstract Exercise is an essential part of the physical and mental health. However, many doctors and patients have a conservative attitude to participate in exercise in patients with congenital heart disease (CHD). Exercise in patients with CHD is a relatively new and controversial field. Taking into account the involvement of exercise in patients with CHD is likely to induce acute cardiovascular events and even sudden death; many doctors have a conservative attitude to participate in exercise in patients with CHD, leading to the occurrence of excessive self-protection. CHD has been transformed from the original fatal diseases into chronic diseases, medical treatment will also transform from the improvement of the survival rate to the improvement of the quality of life. It is still a problem that whether patients with CHD should participate in exercise and which kind of CHD should take part in exercise to improve the quality of life.

Keywords Exercise • Congenital heart disease • Self-protection

1 Introduction

With the advances of medicine, surgery, especially intervention therapy, the survival rate of congenital heart disease (CHD) has been dramatically improved. Nearly 90% patients with CHD can survive to adulthood [1]. The congenital defect of patients with CHD can be repaired well, but the psychological and social problems are always associated with patients throughout their life. Regardless of whether or not to be completely repaired, patients with congenital heart disease often have the high propensity for fear, insecurities, depression, anxiety and low self-efficacy, even it is difficult to get along with their peers. Some of these problems were due to the inherent limitations of patients, but most of them were due to their excessive self-protection. CHD has been transformed from the original fatal diseases into chronic

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diseases, medical treatment will also transform from the improvement of the survival rate to the improvement of the quality of life. How to help patients to complete this transformation has become a new problem in the field of congenital heart disease.

2 Benefit of Exercise in CHD

Exercise is not only required for the development of physical body, but also necessary for the development of emotional and social psychology as well as cognitive skills. Exercise is an essential part of the physical and mental health of healthy people, and patients with CHD. However, due to the misunderstanding, the majority of CHD patients often have psychological conflict. Compared with the same aged healthy people, young patients with congenital heart disease are usually lack of exercise [2]. Lack of exercise and excessive self-protection are very common in patients with CHD [3]. Gupta et al. point out that patients with congenital heart disease have a high degree of potential fear and anxiety. These fears include fear of medical care, fear of injury, fear of death, and so on [4]. Potential fear and rejection can reduce the patient's exercise self-efficacy and increase fatigue, and further reduce the benefits of exercise and physical activity. Many patients with congenital heart disease always shift their attention from exercise to other activities automatically in order to protect themselves. But the sedentary lifestyle associated with self-protection also leads to a decline in physical activity and puts them at risk of early cardiovascular disease and other diseases [5]. A study of patients with CHD after surgical repair showed that the level of physical activity in these patient objectively measured decreased significantly compared with healthy person, and the less physical activity, the lower level of health. In the study of 100 adolescent patients with mild heart dysfunction, self-efficacy is an important factor to participate in physical exercise. It is more important than congenital heart defects, and was affected by heart disease experts and parents attitude [6]. Therefore, self-efficacy is an important determinant of the participation of exercise for patients with CHD. But at present, advice from the experts for patients with congenital heart disease to participate in physical exercise is also ambiguous, which makes it difficult for patients to master the degree of participation in exercise, affecting the patients' self-efficacy and their enthusiasm to participate in exercise [7].

Exercise in patients with CHD is a relatively new and controversial field. Taking into account the involvement of exercise in patients with CHD is likely to induce acute cardiovascular events and even sudden death; many doctors have a conservative attitude to participate in exercise in patients with CHD, leading to the occurrence of excessive self-protection [8]. As we know, exercise can increase the incidence of sudden cardiac death in coronary artery anomalies, cyanotic congenital heart disease and aortic valve disease. But for these patients after successful surgery or with other types of congenital heart disease, it is still unknown whether exercise can increase the incidence of sudden cardiac death. It is therefore not advisable,

even harmful, to recommend that all patients with CHD take an excessive self-protection lifestyle. For example, Shaun White, a patient with tetralogy of fallot after surgery, won the Olympic gold medal twice.

As we all know, compared with the same aged healthy people, exercise tolerance in patients with CHD decreased significantly, and this is why many patients with CHD refused to exercise. However, for the normal population, lack of exercise can also lead to decreased exercise tolerance. Many young patients with CHD have a misunderstanding about the safety and ideal level of sports, which limits their enthusiasm in exercise, and day by day, long-term lack of exercise will inevitably affect the exercise tolerance, while the decline in exercise tolerance in turn will affect the enthusiasm of patients to exercise. This vicious cycle is not only an important reason why patients with CHD lack of exercise, but also an important factor affecting their health [9, 10].

Peak oxygen uptake is an important index to reflect the aerobic capacity of the human body. High peak oxygen uptake is the basis of high level aerobic exercise ability. Patients with CHD are afraid of exercise related complications, and lack of physical exercise result in decreased peak oxygen uptake and exercise tolerance. Research shows that patients with CHD may improve their peak oxygen uptake by exercise. Participation in the safe level of exercise and understanding the benefits of sports is the method to break the vicious circle.

3 Safety of Exercise in CHD

Safety is the primary concern for patients with CHD to exercise. Because the fear that exercise may cause arrhythmia and heart function deterioration, exercise self-efficacy of CHD patients is low, restricting their exercise ability [11, 12]. To eliminate the fear of participating in physical exercise and develop a safe exercise plan is the first step to enhance the participation in physical exercise of patients with congenital heart disease [13–16].

As early as 1984, Freed et al. pointed out the benefits of exercise rehabilitation for patients with CHD [17]. In 2000, Fredriksen et al. proposed that exercise is a new method to improve the quality of life of patients with CHD [10]. Recently, there are accumulating evidence to support the participation in physical exercise of patients with CHD. Jolien W followed up patients with CHD after surgical repair of various types (ASD, VSD, pulmonary artery stenosis, tetralogy of Fallot and transposition of the great arteries) up to 30 years [8, 12]. These patients selected underwent a cardiac examination which consisted of 24-h Holter monitoring, an electrocardiogram, an echocardiogram and exercise testing. The participation in exercise programs, sports and psychosocial characteristics were assessed by questionnaires. And they find there was no significant correlation between exercise and sudden death, ventricular ectopic beats and paroxysmal supraventricular tachycardia. Similar to Buys et al., Ubeda Tikkanen et al., and Muller et al.'s opinion [12, 18, 19], they find regardless of the severity of congenital heart disease, the exercise

tolerance of patients with CHD was significantly higher than those who did not participate in physical exercise. The patients with moderate/severe congenital heart disease who are more physically act is healthier. Patients with CHD after surgical repair do not increase the incidence of adverse cardiac events, and can improve the quality of life and reduce body mass index by participating in physical exercise.

Peter N et al. also conducted a questionnaire survey on the patients with CHD [20]. The questionnaire included exercises types and volume, exercise restriction and children's quality of life scale. Among 177 patients with CHD selected, 31% of the patients were with mild heart disease, 40% were patients with moderate heart disease, and the others were patients with severe congenital heart disease. 52% of these people participate in competitive sports, and 25% involved in recreational sports, while the other 23% of them seldom participate in any sports. It is worth noting that 29% of patients with severe congenital heart disease participated in competitive sports. After eliminating residual hemodynamic disorders, complications and other factors such as age, gender, severity of congenital heart disease, they found that participating in competitive sports and frequent sports can improve the maximum oxygen uptake and slightly lower body mass index. Similar to the results of the Jolien W's study, they also found that participating in physical exercise improves exercise tolerance and quality of life [8].

Therefore, when the evidence for restricting physical exercise is not sufficient, limiting the patient's physical activity is not a reasonable decision [21]. Restricting the patient involved in physical exercise may eliminate the doubts of doctors, patients and families, but it may affect the patient's physical and psychological development. Only a small proportion of sudden death of patients with CHD (10%) occurred during exercise [22]. And whether exercise is responsible for sudden death is still controversial. Even in the case of restricted exercise, the patients who only participate in daily living intensity exercise are still likely to have the chance of sudden death [23]. Restricting physical exercise can't reduce the risk of sudden death, but will affect the patient's quality of life and exercise tolerance and reduce social well-being. Participating in physical exercise can benefit patients with CHD in many ways. First, regular exercise can improve heart function in patients with CHD [10, 24]. Secondly, physical exercise can prevent obesity, and obesity is a risk factor of cardiovascular disease. Thirdly, physical exercise is very important for patients' self-esteem, social integration and academic performance [25, 26]. Regular physical activity can benefit patients, but it does not mean that patients can participate in sports activities with their own willingness. Excessive restriction is as harmful as lack of restriction. So for patients with CHD, exercise programs need to be individualized, neither overly restrictions on physical exercise, nor excessive exercise. Patients with congenital heart disease should choose appropriate exercise with suitable type and intensity [27, 28].

3.1 Assessment

Comprehensive assessment is an important part of the patients with CHD before physical exercise. It is important to make up sports prescription. Six-minute walking test and cardiopulmonary function test are effective tools to evaluate the exercise ability of patients. Twenty four-hour dynamic electrocardiogram and echocardiography are effective tools to evaluate the degree of congenital heart defects and whether they have complications. Successful operation, the presence of pulmonary hypertension, and the postoperative residual defect should also be taken into consideration. Due to the various classification of congenital heart disease, complex clinical situation, and the variation of clinical situation, it is very difficult to develop a unified standard. Exercise prescription for patients with congenital heart disease should be individualized and adjusted according to the changes of clinical condition.

3.2 Recommendations

The patients with atrial septal defect, ventricular septal defect, patent ductus arteriosus, and other shunt congenital heart disease, can participate in any physical exercise if they are not combined with pulmonary hypertension, ventricular enlargement or heart failure. For these patients combined with pulmonary hypertension, but the peak systolic pressure of pulmonary artery is not more than 30 mmHg, they can participate in any sports activities. If the pulmonary artery pressure is greater than 30 mmHg, the patient needs to conduct a comprehensive assessment and make an individualized exercise prescription. These patients with moderate pulmonary hypertension can only participate competitive sports with low intensity, and those with severe pulmonary hypertension or even right to left shunt with cyanosis should not participate in any competitive sports. Patients with cardiac morphological changes (such as enlargement of the left ventricle) due to blood flow shunt should accept surgery or interventional therapy before taking part in the exercise. They can take part in any exercise 6 months after surgery if they are not combined with pulmonary hypertension, symptomatic atrial or ventricular arrhythmias or cardiac dysfunction. If combined with mild heart failure (EF40–50%), they can participate in low intensity static competitive exercise. For those with moderate to severe heart failure (EF less than 40%), they should not take part in any competitive exercise [29].

Patients with no shunt congenital heart disease need to assess the patient's symptoms and transvalvular gradients to formulate reasonable exercise prescription. Pulmonary valve stenosis patients with pulmonary hypertension can participate in competitive sports if transpulmonary valve pressure gradient is less than 40 mmHg and right ventricular function is normal. If the transpulmonary valve pressure gradient is greater than 40 mmHg, the patient can only participate in low intensity of competitive sports. For mild aortic stenosis patients without symptom, patients can

participate in any physical exercise. Patients with moderate aortic stenosis can only participate in the low static/low to moderate dynamic, moderate static/low to moderate dynamic competitive sports. Patients with severe aortic stenosis may not participate in competitive sports [29].

Patients with cyanotic congenital heart disease often combined with exercise intolerance and progressive movement related hypoxemia. They rarely participate in competitive sports. These patients rarely survival to adolescents and adults without movement related hypoxemia, and cyanosis may increase sharply with movement. Untreated patients with cyanotic congenital heart disease should be careful in taking part in exercise. As for postoperative patients with cyanotic congenital heart disease, if the arterial oxygen saturation consciousness was above 80%, without conscious disturbance, arrhythmia and severe cardiac insufficiency, they can participate in low level competitive sports. The patients with anomalous coronary arteries arising between large vessels, especially for those combined with angina or syncope, can't participate in any competitive sports, which can avoid incidence of acute cardiac events [29].

Classification of congenital heart disease is various, and clinical condition is complex. Exercise tolerance and exercise intensity of them are different and restricting exercise is as harmful as excessive exercise. So exercise prescription for patients with CHD should be individualized and adjusted according to the changes of clinical condition.

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Chapter 8
The Positive Effects of Exercise in Chemotherapy-Related Cardiomyopathy

Elena Cavarretta, Giorgio Mastroiacovo, Annik Lupieri, Giacomo Frati, and Mariangela Peruzzi

Abstract Anthracyclines such as doxorubicin, daunorubicin, epirubicin, mitoxantrone and idarubicin, are powerful chemotherapeutic drugs used both in children and adult populations. Their properties made them particularly suitable for a large variety of neoplasms including breast adenocarcinoma, small cell lung cancer and acute leukemia. Early and late anthracycline-induced cardiotoxicity is a well-known phenomenon, and the incidence of heart failure in patients receiving doxorubicin is 2.2%, with a mortality rate over 60% at 2 years. Prognosis can be improved by prevention, early detection and treatment. A specific treatment for anthracycline-induced cardiotoxicity is not yet available, but non-pharmacological measures such as exercise, lifestyle changes and control of risk factors have shown a cardioprotective effect. Exercise training represents a viable non-pharmacological treatment as it increases cardiovascular reserve and endothelial function, regulates proapoptotic signaling, protects against reactive oxygen species (ROS), and decreases autophagy/lysosomal signaling. However, no current guidelines are available for prevention management in cancer patients. Pharmacological measures both for prevention and treatment are those used for heart failure (β-blockers, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, statins, dexrazoxane and aldosteron antagonists). In this chapter, we will discuss how the evaluation, monitoring and prevention of chemotherapy-related cardiomyopathy is correlated with physical exercise.

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Keywords Exercise • Chemotherapy-related cardiomyopathy • Anthracycline • Cardiotoxicity • Prevention

1 Introduction

According to the World Health Organization cancer is the second leading cause of death worldwide, and mortality rates from cancer have declined over the past 30 years [1]. Due to early detection strategies, refined surgical approaches and advances in cancer therapies, the overall survival of oncological patients has increased in the last few years. By 2020 18 million people are predicted to be cancer survivors in the United States [2]. Because of the increasing number of cancer survivors, chemotherapy-induced cardiomyopathy (CIC) is becoming a significant issue. The prevalence of end-stage HF induced by chemotherapeutic agents has increased to 2.5%, and cardiovascular (CV) diseases are the leading cause of long-term morbidity and mortality among cancer survivors [3]. Acute cardiotoxicity is represented by the dawning of hypotension or hypertension; arrhythmias (tachycardia, ventricular premature beats, atrio-ventricular (AV) block, bundle branch block, atrial fibrillation); myocardial infarction; thromboembolism and myocarditis. The most common subacute cardiac adverse effects are pericarditis and myocarditis while the adverse effects of chronic cardiotoxicity are typically dilated cardiomyopathy, left ventricular (LV) systolic dysfunction and congestive heart failure (HF) [4]. Anthracyclines (doxorubicine, daunorubicin, epirubicin, idarubicin and mitoxantrone) are type I drugs most commonly involved in acute, subacute and chronic cardiotoxicity, which is an irreversible and dose-dependent cardiac injury [5]. Dissimilarly, the type II drug trastuzumab is unrelated to the cumulative dose and is often reversible after treatment discontinuation [5]. The molecular mechanisms of cardiotoxicity are still not completely understood, but it seems that the main cause of cardiac injury is mitochondrial damage. This can arise from an increased production of reactive oxygen species) [6], alterations in cardiac energy metabolism [7], ultrastructural changes of cardiomyocytes [8], suppression of myofilament protein synthesis [9] and topoisomerase II beta-mediated DNA damage. Cardiac toxicity is not always clinically symptomatic; therefore, an early diagnosis is crucial for the outcome. The measurement of biomarkers (Troponin I and brain natriuretic peptide (BNP), as well as electrocardiography and echocardiography are all validated methods of investigating CIC. However, none of these methods are effective in detecting sub-clinical myocardial damages induced by chemotherapeutic drugs. Moreover, a specific treatment for CIC is not available, and the therapeutic options remain the ones used for heart failure. Due to the high demand and limited available treatments, a cardioprotective therapy that prevents or treats CIC would be considered advantageous and necessary progress. Among non-pharmacological therapies, aerobic exercise training administered prior to, during and/or following chemotherapy has been shown to safeguard against cardiac injury [10]. The protective effects of aerobic exercise include enhancement of the endogenous antioxidants, regulation of

apoptotic signaling, down-regulation of cardiac autophagy and increased release, mobilization and homing of cardiac progenitor cells [10]. The role of exercise as a possible non-pharmacological treatment for CIC will be further discussed and detailed.

2 Chemotherapeutic Drugs Involved in Cardiotoxicity

2.1 Anthracyclines

Anthracyclines such as doxorubicin, daunorubicin, epirubicin, mitoxantrone and idarubicin are the most frequent antineoplastic drugs involved in cardiotoxicity. They are powerful chemotherapeutic agents administered to children and adult populations [11]. The four main mechanisms by which anthracyclines inhibit cancer cell proliferation are: [1] high-affinity binding to DNA and RNA strands causing intercalation with the subsequent stop of DNA synthesis and final DNA strand separation; [2] inhibition of topoisomerase II, an enzyme necessary for DNA transcription and replication, thus promoting cell apoptosis; [3] generation of free oxygen radicals that produce oxidized DNA bases, promote lipid peroxidation, and finally remove histones from chromatin allowing for genetic and epigenetic dysregulation; and [4] binding to cellular membranes to alter the cell's fluidity and ion transport [10, 12, 13]. Anthracyclines are broad-spectrum anticancer drugs which have shown significant pharmacological activity against several cancers such as stomach, bladder, breast, ovarian, thyroid, small cell lung cancer, acute leukemia, acute myeloid leukemia, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, sarcoma, Hodgkin lymphoma and acute lymphoblastic leukemia [4]. Anthracycline use is limited by its toxic effects that include: cachexia, nausea and vomiting, alopecia, myelosuppression and particularly cardiotoxicity. This latter effect can lead to prematurely halting chemotherapy, therefore increasing the likelihood of cancer relapse [14]. If dose-dependent cumulative and progressive cardiac damage occurs, it will cause LV dilation; therefore, reducing LV systolic function. This will result in a reduced LV ejection fraction (EF) and ultimately cause heart failure (HF) [15]. Therefore, an early-phase reduction in LV ejection fraction must be carefully evaluated, as it is highly predictive of a later cardiomyopathy onset [16]. The incidence of HF in patients receiving doxorubicin at a median dose of 390 mg/m^2 is 2.2%, with a mortality rate over 60% at 2 years [17]. Cardiomyopathy and congestive HF usually develop after numerous cycles of anthracycline over several months. The incidence of cardiomyopathy is reported to be 5% at a cumulative dose of 400 mg/m^2, 26% at a cumulative dose of 550 mg/m^2 and will reach up to 48% at 700 mg/m^2 [18]. The recommended cumulative dose is limited to 450–500 mg/m^2, though a 2% HF incidence was reported at lower doses (<300 mg/m^2) [19]. Theoretically, no dose of anthracycline is absolutely safe, because of unexpected synergic effects related to combination chemotherapy (anthracycline administered in addition to a potentially cardiotoxic biological agent such as trastuzumab) or to thoracic

radiation therapy [20]. Doxorubicin, one of the more common anthracyclines, has detrimental effects on mature cardiomyocytes as well as cardiac progenitor cells and endothelial progenitor cells [21], where the isoform 2 of the superoxide-generating enzyme NADPH oxidase (Nox2) is constitutively expressed. Furthermore, doxorubicin induces ROS production and senescence in a Nox2-dependent manner [22, 23]. Unfortunately, the use of antioxidants such ad N-acetylcysteine has failed to protect patients undergoing doxorubicin treatment from cardiomyopathy [24]. More recently, the isoform 2β of the enzyme topoisomerase has been implicated as a key mediator of AIC since this isoform is found in all quiescent cells, including cardiomyocytes [25]. Anthracyclines target the 2α isoform as it is present in proliferating cells. In cardiomyocytes, inhibition of the topoisomerase 2β causes breaks in double-stranded DNA leading to cardiomyopathy [26, 27]. Levels of the topoisomerase 2β might be a useful marker of an individual sensibility to anthracycline, but large prospective studies are needed to confirm this data [28].

Another relevant molecular mechanism of doxorubin-induced cardiac damage in cardiomyocytes is mediated by autophagy, an evolutionarily conserved cell survival mechanism whereby the cells degrade damaged, altered or unnecessary proteins within the lysosome to maintain cell health and homeostasis [29, 30]. Dysregulation of lysosomal autophagy has been reported in pre-clinical models where doxorubicin impairs transcriptional factors regulating lysosomal function, thereby precipitating proteotoxicity, mitochondrial dysfunction and finally determining cell death, thus rendering the heart susceptible to cardiomyopathic failure [30–33]. Since their discovery, microRNAs, small noncoding 20–22-nucleotide RNAs, have gained momentum as pivotal post-transcriptional gene-regulators and have been implicated in several physiological and pathological events [34] such as coronary heart disease [35, 36], cardiomyopathies [37], heart failure and fibrosis [38–40]. Few studies have described the functional impact of microRNAs in chemotherapy-related cardiomyopathy. Acute, doxorubicin cardiotoxicity has been found to cause the upregulation of miR-146a by targeting ErbB4 3′UTR, inducing cell death in cardiomyocytes [40]. Chronic doxorubicin treatment upregulates miR-208b, miR-216b, miR-215, miR-34c and miR-367 in rat hearts, therefore halting cardiomyopathy [41]. In particular, miR-216b levels increased even at the lowest dose regimen of doxorubicin (1 mg/kg/week for 2 weeks). Roca-Alonso et al. [42] identified the downregulation of the miR-30 family by doxorubicin. The regulation of gene expression by miR-30 seems protective against the toxic effects of doxorubicin in cardiac myocytes, via the β-adrenergic pathway. In fact, chronic adrenergic stimulation in the heart has been shown to elicit cardiotoxicity [43], and β-blocker treatments seem to act protectively toward cardiac progenitor cells [44].

Strategies to limit anthracycline cardiotoxicity have been proposed, such as through the creation of synthetic analogues of natural compounds, i.e. epirubicin and idarubicin. These chemotherapeutic agents are thought to be less cardiotoxic than doxorubicin and daunorubicin, respectively [45]. Furthermore, other strategies to reduce cardiac damage are the use of non-pegylated liposomal doxorubicin [46], and cardioprotective drugs such as the dexrazoxane, an iron chelating agent [47, 48]. Unfortunately, these strategies do not significantly prevent or reduce AIC incidence and mortality.

2.2 *Trastuzumab*

Trastuzumab is a humanized monoclonal antibody directed against the human epidermal growth factor receptor tyrosine kinase HER2 receptor (HER2/neu oncogene), which is overexpressed in 15–25% of breast cancers. By inhibiting the HER2 receptor, trastuzumab prevents epidermal growth factor (EGF) binding, which is an important stimulus for HER2+ cancer cells' proliferation [15]. HER2 is also expressed in the heart, where it is important for cardiomyocyte growth, survival, repair and adaptation to stress [49]. Trastuzumab inhibition of HER2 and HER4 signaling decreases cardiac protection against ROS and induces dilated cardiomyopathy and left ventricular systolic dysfunction [50]. When Neuregulin 1 (NRG-1) binds to HER2/HER4 it is implicated in cardiomyocyte survival and proliferation by promoting myocardial regeneration after injury [51]. In fact, recent clinical studies have shown that the ability of transuzumab to prevent the binding of NRG- 1/ErbB2/ErbB4 complex is crucial for its cardiotoxic effects [52]. In adult human heart, trastuzumab alone causes a contractile dysfunction (dose-independent) without ultrastructural changes (e.g. myofibrillar disarray), which, instead, are typical of the irreversible damage caused by anthracyclines. Moreover, clinical studies have shown that transuzumab induces cardiotoxicity, especially in patients previously treated with anthracyclines [53]. In fact, the incidence of ventricular dysfunction is 3–8% when administered alone, whereas it can increase up to 27% when administered concurrently with doxorubicin [54]. Data from a recent meta-analysis showed that the overall incidence of high-grade HF in patients treated with trastuzumab versus a placebo was 1.44% (95% CI, 0.79–2.64%), and the overall relative risk (RR) was 3.19 (95% CI, 2.03–5.02; $p < 0.00001$), which falls to 2.64 (95% CI 1.61–4.32) for a low-dose trastuzumab treatment (4 mg/kg) [55]. The molecular basis for anthracycline – trastuzumab interaction is complex and involves cellular repair mechanisms that are not yet completely understood. The administration of doxorubicin causes upregulation of HER2 expression in the myocardium, and trastuzumab inhibits pathways that are essential for cell repair. This inhibition can result in increased myocyte death if it occurs during a vulnerable period after anthracycline injury. Trastuzumab could, therefore, exacerbate anthracycline-related myocardial injury [56]. This may explain the lack of recovery from damage that is apparently related to the administration of transuzumab [57]. Numerous clinical studies revealed that hypertension, diabetes and smoking are associated with an increased risk of transuzumab-related cardiotoxicity as well as age (>50) and a left ventricular ejection fraction (LVEF) <55% [58]. However, the most serious risk factor remains the concomitant use of anthracyclines. Clinical features of transuzumab-related cardiotoxicity include arrhythmias, myocarditis, hypertension, myocardial ischemia and heart failure. Other side effects of a trastuzumab treatment include: fever, headache, stomach/abdominal pain, trouble sleeping, nausea, vomiting, mouth sores, and loss of appetite.

2.3 Other Chemotherapeutic Drugs Causing Cardiotoxicity

Other important classes of chemotherapeutic agents that cause arrhythmias, myocardial ischemia, heart failure and myocardial infarction are: alkylating agents (Cyclophosphamide), anthracenedione (Mitoxantrone), antimetabolites (Cisplatino, 5-Fluorouracile, Capecitabine), Vinca alkaloids (Vincristine, Vinblastine and Vinorelbine) and small-molecule tyrosine kinase inhibitors (Sunitinib, Sorafenib, Erlotinib, Lapatinib and Dasatinib) [59]. Additionally, anti-microtubule agents (Paclitaxel and Docetaxel) can damage cardiomyocytes by developing ventricular arrhythmias, syncope, myocardial ischemia and bradycardia [57]. The mechanisms of cardiotoxicity associated with non-anthracycline chemotherapeutics differ among several drugs. Cyclophosphamide at high doses causes permanent heart damage by direct endothelial injury, oxidative stress and mitochondrial damage [60]. The glutathione S-transferase P (GSTP) deficiency is associated with increased accumulation of acrolein-modified proteins in the heart causing arrhythmias and heart failure [61].

Cisplatinum is a potent chemotherapeutic agent causing an acute and cumulative cardiotoxicity which includes symptoms sich as: angina, arrhythmia, myocarditis, acute myocardial infarction, cardiomyopathy and heart failure [62]. Clinical studies showed that Cisplatinum increases the risk of thrombotic events in cancer patients. The mechanism of cardiotoxicity includes direct myocyte injury, production of ROS, oxidative stress, mitochondrial ultrastructural abnormalities, platelet activation and aggregation leading endothelial dysfunction [63]. Interestingly, the plasma levels of cisplatin remain measurable for up to 20 years after completion of therapy. 5-fluorouracil and capecitabine are associated with an incidence of cardiac toxicity that varies from 1 to 68%. Clinical features of toxicity include angina, arrhythmia, acute myocardial infarction, heart failure, cardiogenic shock and QT prolongation with torsades de pointes. The mechanism of cardiotoxicity includes vasospasm, arteritis, coronary artery thrombosis, oxidative stress in myocardiocytes and endothelial cells with an ultimate induction of apoptosis and autophagy, and citrate accumulation leading to a Krebs cycle alteration [62].

Among antibiotics, mitoxantrone is a chemotherapeutic agent that induces an irreversible and dose-dependent cardiotoxicity. Its mechanism of toxicity includes oxidative stress, damage to the mitochondrial respiratory chain and impaired energy metabolism. Mitxantrone stimulates diastolic dysfunction, arrhythmia, ischemic heart disease and chronic heart failure. The chemotherapeutic drug bleomycin induces muco-cutaneous toxicity with pleuro-pericarditis and coronary artery disease caused by its inflammatory effects on endothelial cells [64]. The paclitaxel and docetaxel mechanisms of cardiotoxicity include damage to the Purkinje system or autonomic control, histamine release (with stimulation of specific cardiac receptors and an increased oxygen demand, leading to coronary vasoconstriction and chronotropic effects) and enhanced metabolism of toxic doxorubicin species [65]. Clinical characteristics of toxicity include bradycardia, atrioventricular block, left bundle branch block, ventricular tachycardia and ischemic cardiac events (Table 8.1).

3 Screening for Chemotherapy-Induced Cardiomyopathy

Chemotherapy-induced cardiomyopathy can occur acutely, sub-acutely or even decades after treatment. Uncertainty about the clinical predictors of cardiomyopathy is still existent. Nonetheless, many clinical risk factors are related to the development of anthracycline-associated cardiotoxicity such as age, hypertension, pre-existing cardiac disease and concomitant treatment with other chemotherapeutic agents [66–68]. Particularly for patients who survived childhood cancer, the development of HF later in life is a growing medical issue. Characterizing the high-risk population is necessary to customize their treatment and follow-up. A recent study by Chow et al. [69] followed a large population of 13,060 cancer survivors and, based on the development of sub-sequent HF, assigned them risk scores. Auxiliary information such as age when diagnosed with cancer, sex, and doses of anthracycline and chest radiotherapy, were factored into their scores. The use of this risk score helped to define three groups according to HF incidence at 40 years of age: low-risk 0.5% (95% CI 0.2–0.8), moderate risk 2.4% (95% CI 1.8–3.0) and high risk 11.7% (95% CI 8.8–14.5), however, this method has not been tested prospectively. While risk scores are helpful in deciding which patient needs a closer follow-up, individual variation due to genetic differences needs to be considered [70]. Therefore, the individual risk assessment should include clinical history and previous examinations and baseline measurements of cardiac function and of cardiac biomarkers (N-terminal pro-B-type natriuretic peptide or troponins). Preferably, the same assay should be used as the one during follow-up measurements. A meta-analysis of the predictors of anthracycline cardiotoxicity reported that cumulative dose was the most robust predictor of cardiotoxicity. Chest radiotherapy, African-American ethnicity, very young or very old age, diabetes, hypertension, very high or very low body weight, or severe co-morbidities were found to have acceptable prognostic value for cardiotoxicity [71]. Patients with ≥1 of the previously mentioned risk factors should be offered preventive means that include the accurate identification of risk factors, the use of imaging to discover early toxicity, the use of cardioprotective agents and the administration of drugs for the treatment of HF.

Even in a highly selected cohort of young patients with a low prevalence of comorbidity and cardiovascular risk factors, the number of anthracycline cycles, body surface area, Trastuzumab use and blood pressure ≥140/90 mmHg were independent predictors of subclinical CIC on multivariate analysis [72]. The method of drug delivery may also influence cardiotoxicity. Prolonged infusions of doxorubicin (48–96 h) showed less clinical cardiotoxicity than shorter infusions [73]. Liposome anthracyclines encapsulation is an alternative way of delivering drugs with potentially less cardiotoxicity. Among the primary prevention strategies cardioprotective agents play an important role, as they attenuate the toxic effects of other agents on the heart. Dexrazoxane, an iron-chelating agent, reduces the generation of free-radicals by anthracyclines and is currently clinically approved for use in women with metastatic breast cancer. Probucol, a lipid-lowering agent similar to vitamin E, is also cardioprotective against CIC by acting as an antioxidant factor, increasing

Table 8.1 Main cardiotoxic chemotherapeutic drugs

Chemotherapeutic Agents	Therapeutic Use	Mechanisms of Action	Mechanisms of Cardiotoxicity	Cardiotoxicity	Incidence of Ventricular Dysfunction (%)
Anthracyclines Doxorubicin 400 mg/m^2 Doxorubicin 550 mg/m^2 Doxorubicin 700 mg/m^2	Advanced stomach cancer, Bladder cancer, Breast cancer, Ovarian cancer, Small cell lung cancer, Thyroid cancer, Hodgkin lymphoma, Acute leukemia, Non-Hodgkin lymphoma, Neuroblastoma, Sarcoma	Anthracyclines inhibit helicase, preventing enzymatic cleavage of the DNA double strand and thus interfering with replication and transcription	Main mechanisms: topoisomerase II beta-mediated DNA damage, lipid peroxidation, oxidative stress, apoptosis and necrosis of cardiac cells	Acute: Hypotension, Arrhythmias, Tachycardia, Thromboembolism; Subacute: Pericarditis, Myocarditis Chronic: Dilated cardiomyopathy, Systolic dysfunction, Congestive heart failure	3–5 7–26 18–48
Epirubicin (>900 mg/m^2)	Advanced ovarian cancer, Stomach cancer, Breast cancer, Lung cancer	Redox reactions through formation of cytotoxic free radicals	Combination therapy exacerbates myofilament loss, mitochondrial DNA damage and changes in mitochondrial bioenergetics	Acute: Ventricular tachycardia, AV block, Bundle branch block, Bradycardia, Thromboembolism Chronic: Dilated cardiomyopathy, Systolic dysfunction	0.9–11.4
Idarubicin (>90 mg/m^2)	Acute lymphocytic leukemia, Acute myeloid leukemia	Redox reactions through formation of cytotoxic free radicals.	Disruption of the dynamic regulation of cardiac function, altering adrenergic and adenylyl cyclase activity and calcium homeostasis	Acute: Arrhythmias, Atrial fibrillation, Myocardial infarction, Thromboembolism Chronic: Dilated cardiomyopathy, Systolic dysfunction, Congestive heart failure	5–18

Chemotherapeutic Agents	Therapeutic Use	Mechanisms of Action	Mechanisms of Cardiotoxicity	Cardiotoxicity	Incidence of Ventricular Dysfunction (%)
Mitoxanthone (>120 mg/m^2)	Advanced breast cancer, Acute myeloid leukemia in adults, Non-Hodgkin lymphoma	Redox reactions through formation of cytotoxic free radicals	Disruption of the dynamic regulation of cardiac function, altering adrenergic and adenylyl cyclase activity and calcium homeostasis	Acute: Arrhythmias, Myocarditis, Hypertension, Myocardial ischemia Chronic: Dilated cardiomyopathy, Systolic dysfunction, Congestive heart failure	2–6
Daunorubicin (>120 mg/m^2)	Acute lymphoblastic leukemia, Acute myeloid leukemia	Redox reactions through formation of cytotoxic free radicals	Negative balance of sarcomeric proteins in cardiac cells caused by reduced protein expression and increased myofilament degradation	Acute: Sinus tachycardia, Tachyarrhythmias, Ventricular premature beats, AV block Chronic: Dilated cardiomyopathy, Systolic dysfunction, Congestive heart failure	
Monoclonal antibodies Trastuzumab	Breast cancer HER 2/neu	It inhibits the growth of tumor cell lines hyper-expressing HER2	Antibody-mediated cardiac myocyte damage via ErbB2 inhibition in cardiomyocytes	Acute: Arrhythmias, Myocarditis, Hypertension, Myocardial ischemia Chronic: Congestive heart failure Cardiac injury is not related to the cumulative dose	3–8 given alone Up to 27% when given concurrently with doxorubicin

(continued)

Table 8.1 (continued)

Chemotherapeutic Agents	Therapeutic Use	Mechanisms of Action	Mechanisms of Cardiotoxicity	Cardiotoxicity	Incidence of Ventricular Dysfunction (%)
Bevacizumab	Colon cancer, Breast cancer, Metastatic renal cell cancer	VEGF Inhibition	Antibody-mediated cardiac myocyte damage via VEGF inhibition	Arrhythmias, Hypertension, Congestive heart failure	1–6
Alkylating agents Cyclophosphamide	Breast cancer, Leukemia, Multiple myeloma, Bladder cancer, Ovarian cancer	Free radical damage	Hemorrhagic myocardial necrosis possibly due to free radical damage	Arrhythmias, Hypertension, Pericarditis, Myocardial ischemia, Congestive heart failure	7–28
Protein kinase inhibitors Sunitinib	Stromal tumor of the intestinal tract, Metastatic renal cell carcinoma, Pancreatic neuroendocrine cancers	Induction of myocardial apoptosis	Induction of myocardial apoptosis via multifactorial effects of tyrosine	Hypertension, Myocardial ischemia, Congestive heart failure, Cardiomyopathy	2.7–19

superoxide dismutase activities. An important strategy for primary prevention of CIC is to use neurohormonal antagonists as beta-blockers, ACE inhibitors and angiotensin receptor antagonists [74]. Use of neurohormonal antagonists has not been largely adopted in clinical practice, however, they may be considered for patients who have a high risk of CIC.

3.1 Diagnostic Tools for the Detection of Chemotherapy-Induced Cardiomyopathy

Baseline electrocardiography and echocardiography with the quantitative assessment of LV function is recommended before treatment in all patients, irrespective of clinical history and risk factors, in order to confirm their baseline risk. For low-risk patients, echocardiographic surveillance should be performed every 4 cycles of anti-HER2 treatment or after 200 mg/m^2 of doxorubicin (or an equivalent) for treatment with anthracyclines [75]. More frequent surveillance may be considered in patients with reduced ejection fraction (EF), with structural heart disease at baseline, or in patients with a higher baseline clinical risk (determined by prior anthracycline-based chemotherapy, previous HF or myocardial infarction). Echocardiography is the mainstay, non-invasive method of detecting myocardial dysfunction before, during and after chemotherapy [75]. Two-dimensional echocardiography imaging is the most common technique to detect and quantify systolic LV function. To achieve this, one may calculate the EF utilizing Simpson's rule. Subclinical abnormalities of EF could be missed by two-dimensional echocardiography, unless a critical amount of myocardium has been damaged [76]. Thereofre, real-time three-dimensional echocardiography remains the method of choice to quantify LV EF as it relies on non-geometric assumptions as Simpson's rule [77, 78]. Irrespective of the method used, chemotherapy-related dysfunction is defined as a decrease in the LV EF of >10%, to a value below the lower limit of normal, that must be confirmed 2–3 weeks after the initial diagnosis during a second echocardiographic examination. Consequently, one can confirm a recovery or detect an irreversible dysfunction [79]. Diastolic dysfunction may precede systolic dysfunction, and the use of Tissue Doppler in addition to standard echocardiography has improved the diagnosis of both dysfunctions [80]. Significant temporal changes were found for LV EF and diastolic parameters. The former exhibited a V-shape trend, with an initial decrease and a possible recovery; while diastolic parameters, showed persistent impairments [81]. However, the role of diastolic parameters to detect early subclinical dysfunction remains controversial [11]. Global systolic longitudinal myocardial strain (GLS) has been reported to accurately predict a subsequent decrease in EF and, therefore, should be an additional tool to routine evaluation [82]. A relative percentage reduction of GLS >15% from baseline is abnormal and is considered a marker of early LV subclinical dysfunction [75].

Furthermore, cardiac magnetic resonance with late gadolinium enhancement is a valuable tool in selected cases to determine the cause of LV dysfunction, the presence of inflammation, the occurrence of oedema or the incidence of myocardial chronic diffuse fibrosis [83].

4 Treatment of Chemotherapy-Induced Cardiomyopathy

Administration of both ACE-inhibitors and β-blockers have additive beneficial effects in patients with CIC, and their use is strongly recommended [84]. Another notable therapeutic option for CIC is cardiac resynchronization therapy (CRT) [85]. Clinical studies have shown that there is an encouraging response following CRT implantation in patients with anthracycline- induced cardiomyopathy. It is still unclear if this beneficial effect also impacts non-anthracycline cardiomyopathy.

The mechanical circulatory support is a well-accepted therapy for the treatment of end-stage HF, even in the case of CIC, as an initial support before heart transplantation (bridge to transplant) or as destination therapy. The INTERMACS registry assessed the use of left ventricular assist device (LVAD) among the CIC population [86]. There were no large differences in the use of LVAD among patients with dilated cardiomyopathy due to chemotherapy and other classes of patients. However, in CIC patients there was a more frequent use of a right ventricular assist device. In fact, right ventricular failure was a very common complication in this group of patients. The use of LVAD to help patients with HF (associated with chemotherapy) recover is only in its infancy, as few cases have been reported [87]. Heart transplantation is actually the gold standard of therapeutic options for treatment of end-stage HF. However, in CIC patients this surgical procedure increases the risk of cancer relapse and lowers long-term survival. In the UNOS registry, CIC patients undergoing heart transplantation were more often young females with breast cancer, who required mechanical circulatory support before transplantation [3].

5 Benefits of Exercise in Cancer Patients

Exercise plays a fundamental role in cancer prevention and treatment [88] (Fig. 8.1). In the Physical Activity and Cancer Control Framework, different objectives for exercise programs in each phase (before and after diagnosis) are described [89]. For prevention, there is increasing evidence that exercise (especially long-term, repetitive and strenuous exercise) decreases the incidence of different types of cancer through induced stress and epigenetic mechanisms [90, 91]. Furthermore, a regular physical activity reduces the overall cardiovascular mortality [92]. An epidemiologic review of 73 studies conducted around the world concluded that there was a 25% average risk reduction in breast cancer amongst physically active women as compared to the least active women. The strongest associations were found for

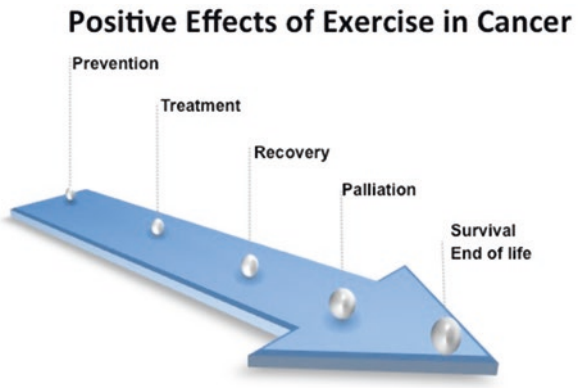

Fig. 8.1 The positive effects of exercise in cancer act at different levels in all phases of the disease, with different aims and exercise protocols per subgroups

recreational activity, for activity sustained over a lifetime or begun after menopause, and for moderate to vigorous intensity activities performed regularly [93]. A recent meta-analysis linking physical activity and renal cancer risk found an inverse relationship with a relative risk (RR) of 0.78 (95% confidence interval, CI = 0.66; 0.92) [94]. Similarly, another meta-analysis concluded that the risk of proximal colon cancer was 27% lower among the most physically active people compared with the least active people (RR = 0.73, 95% CI = 0.66; 0.81). An almost identical result was found for distal colon cancer (RR = 0.74, 95% CI = 0.68; 0.80) [95]. Conversely, spending more than 4 h a day sitting increased the risk of many chronic diseases, including cancer [96, 97]. Moreover, physical activity may not reverse the higher risk of cancer from a sedentary lifestyle [98]. A preoperative high level of physical activity is also associated with a better outcome and reduced need for sick leave after radical prostatectomy in men [99]. Already in 1989, a randomized clinical trial assessed the positive effects of aerobic exercise adjuvant chemotherapy for stage II breast cancer. Aerobic exercise was found to improve functional capacity and body composition of the participants as well as reduce chemotherapy-related nausea [100]. Several other studies have shown the benefits of exercise in reducing the symptoms resulting from chemotherapy, such as shortness of breath and fatigue following completion of the treatment [101, 102]. A systematic review of 4826 patients, from 56 randomized trials to include exercise and control groups, demonstrated that exercise interventions resulted in improvements in quality of life, physical functioning, role function, social functioning and emotional wellbeing. Exercise was also correlated with a greater reduction in depression, fatigue, and sleep disturbances. When examining exercise effects by subgroups, exercise interventions had a significantly greater reduction in anxiety for breast cancer survivors than for those with other types of cancer [103]. In the early survivorship stage after chemotherapy, exercise has been shown to help recover body tissue function, by reducing the effects of both the disease and the treatment [91]. It is important that a physician guides patients in choosing an optimal type and frequency of exercise that will most enhance their recovery, as not all exercise has been found equally beneficially in the early-survivorship stage and subgroups [104]. Moreover, patients in the

early-survivorship phase may have other specific recovery needs related to surgery, radiation or chemotherapy that interfere with physical activity or need a specific rehabilitation program. The current guidelines recommend 150 min of moderate-intensity aerobic exercise and two sessions of resistance training per week [88]. Small volumes of high-intensity activity decrease adiposity and improve insulin sensitivity and inflammation with an hour or less of exercise per week, thus facilitating the perception that physical activity can be enjoyable [105].

In patients with advanced-stage cancer there is a high incidence of decreased physical functioning related to the cancer treatment and the progression of their disease. For these patients, the most prevalent symptom experienced is fatigue, which influences a patient's quality of life immensely by interfering with daily activities. Patients who experience fatigue often also experience decreased memory, generalized weakness, decreased social involvement, emotional lability and have a lower functional status [106]. Physical exercise is safe and feasible for them, even when completed in groups. Furthermore, physical activity may curb functional decline, improve symptom management, encourage living and alleviate common side effects experienced by patients. However, adhering to a routine remains a challenge [107]. There are no standard approaches in an exercise protocol for the palliative care of cancer survivors, but there is growing evidence of exercise's positive effects on life expectancy. More than 30% of total cancer deaths are associated with lack of exercise and malnutrition. Per year, an estimated 250,000 deaths in the US occur due to inactivity, a statistic that would be expected to decrease with specific exercise interventions [108]. In general, high-intensity interval exercise may improve adherence to an exercise routine versus moderate-intensity exercise, which requires longer training to achieve the same health benefits [105].

6 Molecular Basis of Exercise Benefit in Chemotherapy-Induced Cardiomyopathy

To fully understand how exercise can provide cardiac protection against CIC we must focus on the three major molecular mechanisms involved in anthracycline-induced cardiotoxicity:

1. The production of ROS [109–111], which raises oxidative stress levels in cardiomyocytes and activates p53, p38 mitogen activated protein kinase (MAPK) and c-Jun N-terminal kinases (JNKs). These in turn induce cardiomyocyte apoptosis [112–115].
2. The alteration of cardiomyocyte morphology by ultrastructural changes and suppression of myofilament protein synthesis. Ultrastructural changes are induced by a boost release of calcium and the inhibition of its reuptake by the sarcoplasmatic reticulum. These events lead to an intracytoplasmatic calcium overload and subsequently to systolic/diastolic dysfunction. The dysfunction occurs by stimulating the release of the proapoptotic factor cytochrome c and by activating

the cysteine protease calpain, which cleaves and regulates structural myofibrillar proteins [8, 116, 117]. The suppression of myofilament protein synthesis is generated by the depletion of cardiac progenitor cells (CPC) and the down-regulation of GATA-4, which is a CPC transcriptional factor essential for postnatal cardiomyocyte survival. This leads to the inhibition of sarcomere protein synthesis, the increase of senescent cardiac cells and ventricular dysfunction [9, 118, 119].

3. The alteration in cardiac energy metabolism produced by the reduction of ATP and phosphocreatine levels and AMP- activated protein kinase (AMPK) activity. These events lead to a lack of acetyl-CoA carboxylase, resulting in impairment of fatty acid oxidation [7, 120].

In 1979, Combs et al. published the first study that evaluated the role of exercise in CIC [121] in a mouse model. They tested the effect of the administration of 18 or 23 mg/kg of Adriamycin by making the mice swim for 30 min after administration. Thirty days later, the survival of the exercise group was no different compared to the control group (sedentary animals). Therefore, they demonstrated that exercise stress does not increase Adriamycin toxicity. More recent studies by Kanter et al. [122] and Ji and Mitchell [123] investigated the role of exercise in preventing ROS formation and in reducing cardiac oxidative stress induced by anthracycline. In the earlier study [122], mice receiving doxorubicin (4 mg/kg; 2 day/week for 7 weeks) were divided in two groups: mice that underwent exercise (60 min/day; 5 day/week for 21 weeks), and sedentary mice. After 21 weeks, the mice that had been training, regardless of drug status, had elevated levels of blood catalase (CAT), liver CAT, superoxide dismutase (SOD), and glutathione peroxidase (GP). Moreover, the degree of cardiotoxicity was significantly greater in the sedentary drug-treated animals than in the swim-trained, drug-treated animals [122]. In 1994, Ji and Mitchell [123] investigated the effect of adriamycin administration (bolus 4 mg/kg; twice) on cardiomyocyte mitochondria in rats at rest and after acute exercise (60 min). The main finding was that adriamycin can interfere with normal heart mitochondrial function both at rest and during heavy exercise. The mitochondrial respiratory control index was decreased with adriamycin administration, but the reduction was due to an increase in state 4 rather than a decrease of state 3 (ADP-stimulated) respiration. These two studies opened the door to numerous others that have attempted to understand the role of exercise in the prevention of ROS formation in CIC. Ascensao et al. [124, 125] compared the effect of a bolus of doxorubicin (20 mg/kg) in trained mice (60–90 min/day; 5 day/week; 14 weeks before doxorubicin) to sedentary mice as controls. Doxorubicin elevated levels of plasma cardiac troponin I (cTnI), oxidized glutathione, thiobarbituric acid reactive substances, carbonyl groups and heat shock protein (HSP) by 60%. Endurance exercise significantly increased levels of total and reduced glutathione, increased HSP60 expression, and reduced the rise of plasma cTnI. These changes result in an improvement of the mitochondrial and cell defense systems and a reduction of cell oxidative stress. This latter reduction occurs by the increased activity of both cytosolic and mitochondrial antioxidant enzymes such as Glutathione 1, CAT and SOD and by the increased level of HSP 60 and 70. HSP 60 and HSP 70 are known to attenuate lipid peroxidation and preserve cardiac

function by: controlling protein folding, preventing protein denaturation and aggregation and accelerating the breakdown of the damaged proteins. In addition, Werner et al. [126] showed that AET prevents cardiomyocyte apoptosis by diminishing doxorubicin-induced p53 expression. Endurance training limited the doxorubicin-triggered apoptosis by decreasing mitochondrial levels of protein carbonyl groups, malondialdehyde, Bax, Bax-to-Bcl-2 ratio and tissue caspase-3 activity. A further study by Chicco et al. [127] demonstrated that low intensity exercise training decreases activation of the apoptotic pathways and cardiac dysfunction induced by doxorubicin, whereas it increases GP expression. No significant positive effect on lipid peroxidation or SOD isoforms was detected. Further studies by Chicco et al. [128, 129] compared rats that had undergone free wheel-runs for 8 weeks to sedentary controls. These studies showed that chronic physical activity provided resistance against doxorubicin cardiotoxicity by increasing the level of HSP72 by 78% in the cardiac tissue of exercising rats. Moreover, LV systolic contractility and LV relaxation rates were, respectively, higher and faster in endurance-trained animals. More recent studies have validated these findings [130, 131]. Particularly, a Shirinbayan et al. study demonstrated that exercise prior to doxorubicin exposure significantly increased cardioprotective markers (SOD and HSP70) and decreased cardiac toxic ones such as malondialdehyde, creatine kinase and creatine phosphokinase [132]. One of the most relevant side effects of AIC is the reduction of CPC differentiation and proliferation. A study conducted by Kolwicz et al. [133] demonstrated that exercise significantly increased the number of CPC in hearts, while a different study by Bostrom et al. [134] determined that exercise increased levels of mRNA GATA-4, an important transcriptional factor for cardiomyocyte survival. According to these two studies, aerobic exercise prevents ROS formation, limits oxidative stress, and abates the suppression of myofilament protein synthesis. Furthermore, multiple experiments by Hydock et al. [135–138] suggested that exercise training in rats before and during the administration of doxorubicin maintains high levels of α- myosin heavy chain (MHC) isoform in cardiac cells more than in the sedentary control rats. This is one of the various cardioprotective mechanisms of exercise that fights the effects of anthracycline since an increase in β-MHC isoform is associated with HF. In an additional study that compared rats that exercised on treadmills and wheels with sedentary rats, exercise helped prevent LV dysfunction and the reduction of mitral and aortic valve blood flow velocities typically induced by doxorubicin [136]. A further positive effect of exercise on the heart muscle is the activation of AMP-activated protein kinase (AMPK). One of the best-characterized downstream targets of AMPK is acetyl-CoA carboxylase. Its phosphorylation inhibits malonyl-CoA synthesis, enhancing carnitine palmitoyl-transferase I activity and free fatty acid oxidation [139]; nevertheless, this beneficial effect of exercise has not yet been tested after doxorubicin administration in animals. Preclinical studies suggest that aerobic exercise has an important protective role on the cardiovascular system by countering different AIC pathways (Fig. 8.2):

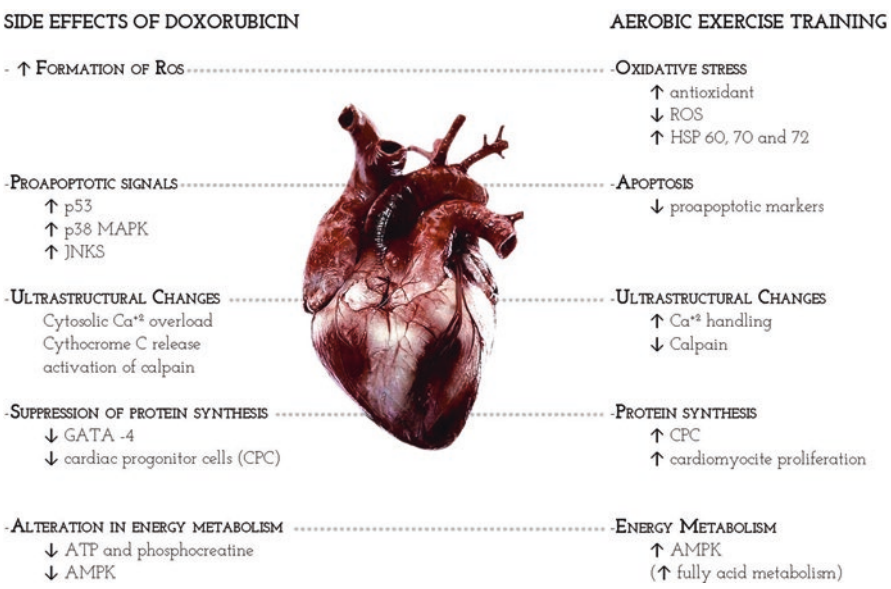

Fig. 8.2 Side effects of doxorubicin and potential benefic effects of aerobic exercise training in the prevention of chemotherapy-induced cardiomyopathy (*AMPK* AMP-activated protein kinase, *ATP* adenosine triphosphate, Ca^{32+} calcium, *CPC* cardiac progenitor cells, *HSP* heat shock protein, *JNKS* c-Jun N-terminal kinases, *ROS* reactive oxygen species)

1. Exercise protects against ROS production by enhancing the production of SOD, HSP 60, 70 and 72 and by decreasing proapoptotic signaling from Bax, caspase 3 and p53 expression.
2. Exercise helps stimulate the proliferation and mobilization of CPC (cKit+) and helps increase levels of GATA-4 mRNA, which is important for reestablishing the ultrastructure of cardiac microfilaments. This ultimately prevents a calcium overload.
3. Exercise increases levels of AMPK, resulting in improved cardiac metabolism so that both ATP and creatine phosphokinase levels increase.
4. Exercise promotes cell survival by preventing the high levels of autophagy/lysosomal signaling usually induced by doxorubicin [140].

In conclusion, the main mechanisms used to protect the body from CIC are to enhance antioxidant defenses and inhibit apoptosis. Exercise prevents systolic and diastolic doxorubicin-induced dysfunction, decreases cardiomyocyte damage, increases cell survival rate and decreases pro-apoptotic markers [141]. The preclinical studies suggested that exercise is an appealing and recognized, supportive therapy to prevent CIC. Further studies will be necessary to investigate if these cardioprotective effects of exercise are reproducible in humans.

7 Clinical Studies

There have been few studies that investigate the role of aerobic exercise training in patients undergoing chemotherapeutic cardiotoxic drugs. Most of them are randomized, clinical trials evaluating the role of exercise in women treated with anthracyclines against breast cancer. A series of studies by Courneya et al. have looked at this issue [142–144]. In a multicenter, randomized trial, 242 breast cancer patients beginning adjuvant chemotherapy were randomly assigned to usual care, supervised resistance exercise, or supervised aerobic exercise for the duration of their chemotherapy. The results suggested that both aerobic and resistance training did not significantly improve health related quality of life (HRQoL), but they ameliorated several aspects within the population, including: self-esteem, physical fitness, body composition, and chemotherapy completion rate. Furthermore, they did not cause lymphedema or any significant adverse events [142].

Consequently, in contrast to their previous findings, Courneya et al. [143, 144] demonstrated that aerobic exercise can in fact improve the quality of life of women with breast cancer. They examinined the effect of different exercise protocols in 301 women receiving chemotherapy with Herceptin or taxane. Patients trained 3 days a week for a standard 25–30 min of aerobic exercise, for a higher 50–60 min of aerobic exercise, or for a combined 50–60 min of aerobic and resistance exercise. Data showed that higher volumes of exercise (aerobic or resistance) improved sleep quality during breast cancer chemotherapy, lessened declines in physical functioning and decreased any worsening symptoms.

A study conducted by Hornsby et al. [145]. supports this hypothesis. The authors randomly assigned 20 patients with stage IIB-IIIC operable breast cancer to receive doxorubicin alongside cyclophosphamide or cyclophosphamide in combination with a 12-week aerobic exercise routine. The study found that moderate-to-high intensity aerobic training, when conducted with one-on-one supervision, is a safe adjunct therapy associated with improvements in cardiopulmonary function and in patient-reported outcomes during neoadjuvant chemotherapy [145].

Vincent et al. [146] investigated the role of a 12-week home-based walking exercise program in 39 breast cancer patients (predominantly stage II cancer) receiving adjuvant chemotherapy. The home-based walking program was deemed feasible and was associated with significant improvements in percentages of maximal oxygen uptake (VO_2max), with no significant effect on the fatigue score. Finally, Haykowsky et al. [147] examined the effect of aerobic exercise in trastuzumab-related changes in women with HER2-positive breast cancer. In this study, peak exercise heart rate, systolic and diastolic blood pressure, power output and oxygen consumption were evaluated. The main finding was that aerobic exercise did not ameliorate LV dilation or ejection fraction. By summarizing these findings, it becomes apparent that overall, aerobic exercise improved HRQoL and physical activity in patients with CIC and may be a valid therapy, either for the treatment, or for the prevention of CIC. Moreover, it seems that the most effective form of exercise is the one supervised by a trainer.

An important finding is that even if high intensity training demonstrated to have more beneficial effects than a more leisurely, standard training, workouts to be completed at home that take only 20 min per day, 3 days a week, resulted in important positive effects [137]. Nevertheless, there is still no official exercise protocol for cancer patients, and further studies are needed to clarify the most appropriate forms of exercise.

8 Exercise Prescription

Healthy adults are encouraged to exercise moderately for 150 min/week or vigorously for 75 min/week [148], and The American College of Sports Medicine's exercise guidelines for cancer survivors recommends a protocol adapted to the abilities of individual cancer survivors [88]. Unfortunately, few data exist that are cancer-specific. Moderate intensity is classified as a person reaching 64–76% of maximal heart rate (HR_{max}), and if no measured HR_{max} is accessible, age-predicted maximum heart rate (220-age) may be used [148, 149]. Other parameters are VO_2max and heart rate reserve (HRR, which is the difference between resting heart rate and HR_{max}). However, one study found that 50% of breast cancer survivors experience resting sinus tachycardia up to 20 months after anthracycline and/or trastuzumab chemotherapy, and 46% of patients were classified with low cardiorespiratory fitness [150]. Therefore, prescribing exercise by using HRR or VO_{2max} may be inaccurate. Specifically, using HRR may result in exercise that is too intense for patients, while using VO_{2max} may lead to an exercise intensity below patient needs. On the other hand, HR_{max} seems to be an appropriate parameter [151]. Furthermore, LV function must be carefully evaluated, using quantitative LV EF, tissue Doppler imaging and global longitudinal strain data. One must also take into account subclinical damages, as up to 10% of patients may present a LV EF <50% with a reduced exercise-tolerance. It is recommended to perform echocardiographies and cardiopulmonary stress tests after each cycle of chemotherapy, to assess clinical heart status and improve exercise protocol as tolerated by each patient [141].

9 Conclusion

Physical exercise is a powerful, supportive therapy for the prevention of chemotherapy-induced cardiomyopathy. Existing studies mainly focus on doxorubicin cardiotoxicity. In future research, it will be important to investigate toxicity of other chemotherapeutic agents, particularly when administered concomitantly. Furthermore, larger trials are needed to better define an adequate exercise prescription and the proper frequency, intensity and timing of physical exercise for the prevention of chemotherapy-induced cardiomyopathy. However, the studies completed thus far have laid out solid foundations to build from so that future research has a highly promising outlook.

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Chapter 9
Clinical Evidence of Exercise Benefits for Stroke

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Abstract Even though stroke is the third, not the first, most common cause of disability-adjusted life years in developed countries, it is one of the most expensive to treat. Part of the expense is due to secondary problems in the post-stroke period including: cognition, memory, attention span, pain, sensation loss, psychological issues, and problems with mobility and balance. Research has identified that exercise has both positive physical and psychosocial effects for post-stroke patients. Therefore, this scientific statement provides an overview on exercise rehabilitation for post-stroke patients.

We will use systematic literature reviews, clinical and epidemiology reports, published morbidity and mortality studies, clinical and public health guidelines, patient files, and authoritative statements to support this overview.

Evidence clearly supports the use of various kinds of exercise training (e.g., aerobic, strength, flexibility, neuromuscular, and traditional Chinese exercise) for stroke survivors. Aerobic exercise, the main form of cardiac rehabilitation, may play an important role in improving aerobic fitness, cardiovascular fitness, cognitive abilities, walking speed and endurance, balance, quality of life, mobility, and other health outcomes among stroke patients. Strength exercise, included in national stroke guidelines and recommended for general health promotion for stroke

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survivors, can lead to improvements in functionality, psychosocial aspects, and quality of life for post-stroke patients. Flexibility exercises can relieve muscle spasticity problems, improve motor function, range of motion, and prevent contractures. Stretching exercises can also prevent joint contractures, muscle shortening, decrease spasticity, reduce joint stiffness and improve a post-stroke patient's overall function. Neuromuscular exercises can improve activities of daily living (ADL) through coordination and balance activities. Traditional Chinese exercises are used to improve walking and balance ability as well as increase muscle strength, which is important for post-stroke patients.

The present evidence strongly supports the power of exercise for post-stroke patients, which in this study combined aerobic exercises, strength training, flexibility exercises, neuromuscular exercises, and traditional Chinese exercises. This research can encourage post-stroke survivors to consider the importance of exercise in the rehabilitation process.

Keywords Clinical evidence • Exercise • Stroke

Transient ischemic attack (TIA), ischemic stroke, and intracerebral hemorrhage are all terms used to describe a stroke. Once a patient has had a stroke, there is an elevated risk for future vascular events and this risk is increases even more in those with cardiac-cerebral vascular disease.

Compared with other cardiovascular diseases, a stroke is the third largest cause of disability-adjusted life years in developed countries. Approximately 0.4% of Western country population have had stroke by the age of 45. Around half of those who have experienced a stroke have a lifelong disability. In addition, the incidence of stroke has increased because of the global population growth, the obesity epidemic, diabetes, heart failure, and the overall lack of physical activity among the general population. In the United States, the prevalence of stroke has increased by almost 25% since 2010. It is predicted that an additional 4 million people will suffer a stroke by 2030, which contributes to the country's overall healthcare costs.

Post-stroke improvements in the individual vary due to the nature and severity of the primary deficit. It is reported that up to 35 percent of stroke survivors with initial leg paralysis are unable to regain physical function and 20–25 percent are unable to walk without full physical assistance. Six months after a stroke, about 65 percent of patients are unable to incorporate the affected hand into their daily activities. In addition, there are several post-stroke long-term physiological, mental, and psychological problems, including movement and function, balance, pain, sensation, perception, cognition, attention, memory, and emotional problems. About half of post-stroke survivors report that their stroke-related problems are unmet. Therefore, effective stroke rehabilitation is an indispensable part of stroke care.

This overview will address if exercise benefits are meaningful to stroke patients. It will also review how the effects from exercise align with the needs of stroke survivors. In the 2014 Scottish Stroke Nurses Forum (SSNF), 10 post-stroke priorities were identified and the most important intervention that was repeatedly mentioned was exercise [1].

Exercise can positively influence several physical and psychosocial domains after a stroke. After a stroke, evidence shows that exercise can improve cardiovascular fitness, walking ability, and muscle strength. Exercise has primarily been used to improve physical function after stroke, but emerging research suggests that exercise may improve depressive symptoms, some executive functioning, memory, fatigue, and other health-related quality of life for post-stroke patients.

Post-stroke patients can benefit from exercise training; however, most healthcare professionals lack experience in exercise programming in this patient group. Therefore, this scientific statement will help to fill the current post-stroke exercise rehabilitation knowledge gap. Thus, the aim of this section is to detail the effects of various kinds of exercise rehabilitation in post-stroke patients.

1 Benefits of Aerobic Exercise in Post-Stroke Patients

In the past decade, post-stroke aerobic exercise has gained more attention and recognition from both clinicians and researchers. Aerobic exercise training plays a vital role in promoting aerobic fitness, cardiovascular fitness, cognitive, walking speed and endurance, balance, mobility, quality of life, and other health outcomes among post-stroke patients. The American Heart Association (AHA) also recommends regular aerobic exercise as part of stroke prevention and treatment [2]. Aerobic exercise, the main part of cardiac rehabilitation, is an integral part of stroke rehabilitation and cannot be considered a substitute for conventional drugs or surgery treatments. Recent research reports that the influence of aerobic exercise for post-stroke patients and the need to implement post-stroke exercise programs is crucial.

1.1 Cardiorespiratory Fitness

It is reported that a person with a low cardiorespiratory fitness level has an increased risk of a having a stroke. Even though higher levels of cardiorespiratory fitness to lower a person's stroke risk have not been well established, aerobic exercise can improve cardiopulmonary fitness in post-stroke patients. Systematic reviews [3–5] in recent years have showed that aerobic exercise can enhance the elasticity of the heart and lung, which is effective in improving peak VO2, 6 meter walk test (6MWT), forced vital capacity (FVC), peak workload, and other cardiopulmonary functions in stroke patients. For example, Globas et al. [6] used treadmill walking starting at a 40–50% heart rate reserve (HRR) and then up to a 60–80% HRR, initially 10–20 min

and up to 30–50 min, respectively, 3 times per week for a total of 13 weeks. They discovered that a peak VO2 (measure of the maximum volume of oxygen) increased by 29% and the 6 MWT increased by 21% after 3 months of exercise. Lennon et al. [7] studied the peak heart rate achieved during an exercise test as an outcome. Intervention courses attended 30-min cycle ergometry exercise using the upper or lower limbs twice per week for a 10-week duration. Lennon et al., set a maximal heart rate of 50–60% as a biofeedback alarm during exercise. The primary outcome measures were cardiac risk score (CRS); VO2 (mL O2/kg per minute) and a Borg Rate of Perceived Exertion (RPE) during a standardized ergometry test. The results revealed that group comparison with independent t-tests were significantly improved compared to the control group in VO2 and CRS at follow-up. Of note, the RPE rating decreased in intervention individuals and increased in the control group.

In clinical practice, aerobic exercise has been suggested to become a positive, task-oriented intervention to promote cardiovascular fitness. Cardiorespiratory fitness with aerobic exercise training protocols of at least 8–12 weeks (intensity 50–80% of HR(max); 3–5 days per week; 20–40 min) has helped to improve the lives in patients who have experienced a mild to moderate stroke.

1.2 Cognitive Function

Over a third of stroke patients exhibit permanent sequelae of cognitive impairment [8]. Cognitive deficits resulting from a stroke, even from a mild impairment, can have a negative effect on physical rehabilitation, social functioning, and independence and are also associated with long-term morbidity and disability. Therefore, it is necessary to find effective treatments for cognitive impairment in individuals who have suffered a stroke. Recent meta-analyses confirmed that aerobic exercise can enhance cognitive performance in a healthy population [9]. In addition, many systematic review studies in post-stroke patients involve aerobic training [10, 11]. For example, Cumming et al. [11] conducted a systematic review to evaluate the effects of physical activity on cognitive function in stroke survivors. They included all controlled clinical studies and randomized controlled trials that assessed the influence of physical activity or exercise on cognitive function in stroke. The literature search found evidence that increased physical activity can improve cognitive performance in stroke survivors. Exercise can improve oxygen consumption, increase cerebral blood flow, and promote brain cell regeneration in the encephalic regions related to cognitive function.

Cognition is not a unitary concept because it incorporates many other aspects, including executive function, attention, visuospatial ability, memory, and language [12]. Attention, visuospatial ability, and language were reported in a El-Tamawy et al. [13] study of thirty stroke patients. They were divided into two groups: (G1) received a conventional physiotherapy program and (G2) performed aerobic exercise in addition to a routine program. Then, they compared the cognition function between the 2 groups using the Adenbrookes's Cognitive Examination-Revised (ACER) assessment. The study showed a significant improvement in ACER atten-

tion scores. A pilot study also described changes in measures of executive function in long-term stroke patients following aerobic and strengthening exercise [14]. In this study, nine stroke patients completed a 12-week aerobic and strengthening exercise program that occurred 3 days per week. Executive function was examined by Digit Span Backwards and Flanker tests. The results showed significant improvements following the intervention in the Digit Span Backwards test and a significant correlation on the Flanker test. To decide if a combined exercise could improve the memory of long-term stroke patients, 11 ambulatory participants with chronic stroke took part in a program of exercise for 2 h and recreation for 1 h weekly for 6-months [15]. They, then evaluated the memory of the study participants (Rey Auditory Verbal Learning Test—long delay) at baseline and at 3 months and found that the mean improvement was 61% ± 69, which indicates that exercise and recreation may improve the memory of stroke survivors. Further clarification is needed to determine which types of exercise interventions can benefit cognitive function following a stroke.

1.3 Functional Performance

More than 50% of stroke survivors report gait disability or an abnormal gait pattern [16]. The multiple physical impairments that can result from a stroke may lead to a physically inactive lifestyle and induce a vicious cycle of deficient physical function. Therefore, aerobic exercise training may break the vicious cycle of physical inactivity and functional decline, and have an important effect on improving the functional performance of stroke patients.

1.3.1 Balance

Aerobic exercise has beneficial effects on the balance function of stroke patients. In clinical trials, balance scales (e.g., Berg balance score, [BBS]) and balance tests (e.g., Timed Up and Go Test [TUGT] the Four-Square Step Test, and Functional Reach Test) are commonly used to assess balance. A recent review study [4] reported a significant balance improvement following 4 weeks of 20–30 min of cycling or body weight supported treadmill training. Gama et al. [17] conducted a study with 28 subjects with hemiparesis and divided them into two groups. The participants underwent partial bodyweight-support treadmill training for the twelve 20-min training courses 3 times per week. After the 12 training sessions, the participants were assessed the balance by the BBS. The study reported that 8 weeks of moderate aerobic exercise significantly improved functional balance. To understand aerobic exercise-induced improvements in balance function after stroke, Quaney et al. [18] had 38 chronic stroke survivors randomized to 2 different groups who exercised 3 times a week (45-min sessions) for 8 weeks. The aerobic exercise group (n = 19; 9 women; 10 men; 64.10 ± 12.3 years) did a stationary bicycle training program,

while the other group did a stretching exercise program (n = 19; 12 women; 7 men; 58.96 ± 14.68 years) by doing stretches at home. Participants in the aerobic exercise group performed stationary bicycle under the supervision of a physical therapist and exercise physiologist with an aerobic exercise target level equal to 70% maximal (max) heart rate (HR) for 45 min (based on Karvonen's formula), 3 times per week for 8 weeks. At the end of the 8-week study, changes in performance at "post" and "retention" (8 weeks later) for neuropsychological and motor function between the two groups were measured. The BBS measured balance and coordination while standing and sitting, a trend toward significance in BBS Control was observed at 8 weeks after baseline and then reached significance at 16 weeks after baseline. A 3-month aerobic training program showed a significant improvement in the balance ability of stroke patients. In the Batcho et al. study [10], a total of 44 stroke patients were recruited in a European high-income area (Belgium) and in an African low-income country (Benin). The 3-month exercise intervention included a 3 times/week group-based brisk walking program. Study participants had to walk at their fastest pace on a regular surface. It was reported that the study participant's balance function improved significantly after this intervention.

Aerobic exercise has beneficial effects on stroke patients' balance function, regardless of the training type, intensity (mild, moderate or high), and duration (3–5 days per week; 4 weeks to 3 months).

1.3.2 Walking Speed

Disability from a stroke can lead to a sedentary lifestyle and may induce long-term physical deconditioning and interfere with walking ability. It also can lead to further decline of cardiovascular fitness. Poor cardiovascular fitness has been associated with a higher stroke risk and stroke mortality. Most studies have found that aerobic exercise training can improve walking speed [3]. Thirty-eight subjects who had suffered a stroke over 6 months and who had residual hemiparetic gait were enrolled in the Globas et al. [6] study. To compare the effects of 3 months (39 sessions) and test the efficacy of aerobic treadmill exercise (TAEX) with usual care physiotherapy (control) according to the typical German prescription (1–3 sessions/week), they adopted a randomized controlled design. The primary outcome measure was a sustained walking capacity in the 6 MW. The secondary measures were gait velocity during a 10-min walk. Thirty-six participants completed the study (18 TAEX, 18 controls), which showed that TAEX, and not conventional care, improved the 6 MW (53 m, $P < 0.001$). In addition, the maximum walking speed (0.13 m/s, $P = 0.010$) also improved after TAEX. Better walking was related to a progression in treadmill velocity and training duration. Compared to the baseline, 6 MW performance remained high even 1 year after the end of training. This trial shows that TAEX can improve gait and cardiovascular fitness effectively in post-stroke individuals.

The improvement in walking speed may be due to repeated gait practice at a higher speed. An improvement in maximum walking speed was significantly

related to a progression of treadmill velocity and training duration. Previous aerobic exercise intensity studies reported that even at the low end-range of the targeted heart range (HR) and increased in intensity, progressions were reported in brachial artery vasomotor reactivity as well as walking speed [19], was set to maintain HR between 50 and 59% of HR reserve for weeks 1–4 and increased to 60–69% during weeks 5–8. The exercise duration began at 20 min with a final goal of 30 min of persistent exercise at a specified workload. A peak exercise test evaluated exercise capacity and found that the mean exercise test time increased from the initial assessment at baseline. At the 1-month follow-up, only peak watts and RPE maintained a significant difference from baseline. However, further walking speed improvements after exercise may be more distinct if the participants perform a more scheduled walking task [3].

1.3.3 Endurance

Endurance is a difficult issue for post-stroke individuals. The meta-analysis [3, 4] also showed that aerobic exercise is effective in inducing walking endurance. One 4-week study [20] compared intensive aerobic exercise for 30 min a day to traditional physical therapy that occurred once per day for 5 days per week. The controlled group performed an aerobic exercise for 30 min and the other group had a physical therapy session for 30 min a day, 5 days a week. After the intervention, the two groups measured the forced vital capacity, forced expiratory volume in 1 s, 10-m walking test, and 6-min walking test. After the intervention, the comparison between the two groups showed that the experimental group achieved more significant improvements in the forced vital capacity, forced expiratory volume in 1 s, and 6-min walking test. The results indicate that intensive aerobic exercise had a positive role in respiratory capacity and walking endurance in post-stroke patients. Another study [21] of 28 patients who had experience a post-minor ischemic stroke in the previous 1–3 weeks were randomly divided into intervention or control groups. The 6-week intervention training consisted of a session of 35–55 min on a treadmill, a hand bike machine and a bicycle, twice a week for 3 h a week, and the pulse rate target was set at 50–70% of the maximal heart rate. The per protocol analysis found a significant interaction effect, but only in the intervention group participants as they showed a significant clinical change in the 6 MWD test (412 ± 178 m to 472 ± 196 meters vs. the control group 459 ± 116 m to 484 ± 122 m $p < 0.01$).

Aerobic exercise can improve endurance in post-stroke patients, regardless of the training type, intensity (mild, moderate or high), and duration of the intervention. Aerobic exercise can improve can improve physical function and allow patients to return to their family and community (Table 9.1).

Table 9.1 Optimal parameters to affect stroke outcomes

Outcomes	Frequency	Duration	Intensity
Cardiorespiratory fitness	3–5 days/week; 20–40 min/per day	8–12 weeks	Moderate-high
Cognitive function	>3 days/week; about 30 min	Over 4 weeks	Unknown
Functional performance			
Balance	3–5 days/week; 20–30 min	4 weeks to 3 months	Mild-high
Walking speed	3–5 days/week; 20–30 min	8–12 weeks	Mild-moderate
Endurance	3–5 days/week; 20–30 min	4–6 weeks	Mild-high

2 Benefits of Strength Exercise

Strength exercise, also known as resistance exercise (RE), as a form of rehabilitation, has been included in national stroke guidelines and is recommended in post-stroke patients to improve their overall health.

Muscle weakness is a common physical impairment and a leading target of secondary injury following a stroke [22]. Even though, strength exercises remain an understudied and underappreciated exercise modality for stroke patients when compared to aerobic exercises, Strength training can improve functionality, psychosocial aspects, and the quality of life in stroke individuals. Resistance exercise is used in rehabilitation programs to improve muscle strength [23], thereby improving functional ability and the overall quality of life.

2.1 Improve Muscle Strength and Endurance

Muscle tissue loss caused by secondary stroke injury and from a sedentary post-stroke life-style can lead to metabolic and endocrine related disorders. Two studies reported positive effects on muscle strength after 10–12 weeks of progressive resistance training compared to a control group, with a 30–70% increase in knee extension or flexion and a 15–35% increase in plantar flexion of the ankle. Lee and Kang [24] found that isokinetic eccentric resistance exercise (8 repetitions per set for 4 sets, 60 min per day, 3 days per week for 6 weeks, at an angular velocity of 90°/sec) can improve hip muscle strength. Vinystrup et al. [25] found that by increasing velocity (full available range of motion (ROM) for 3 repetitions at a 10 repetition max (RM) load) during heavy resistance knee flexion exercise improved muscle activity levels. Furthermore, Frederick et al. [26] found the participants who accepted strength exercise (2 sets of 20 repetitions on each leg, 45 min per day, 3 days per week for 3 months) had a significantly greater skeletal muscle endurance ability compared to a control group in both the paretic (178% vs. 12%) and non-paretic legs (161% vs. 12%). Kim et al. [27] also reported positive effects on muscle strength after 10 weeks of strength training for the lower extremity, but did not find a significant difference between the intervention and control group.

2.2 Improve Walking Performance and Balance

Since, muscle strength is closely associated with walking performance [28], one purpose of stroke rehabilitation is to improve muscle strength and thereby enhance walking ability [29]. Most of the RE studies reported a positive improvement in walking performance. Another meta-analysis suggested that performing a lower limb resistance training program in community-dwelling patients who had a stroke after 6 months improved their gait speed and total distance walked [30]. Similarly, a 2008 review proposed that resistance training increases strength, gait speed, and functional outcomes, and improves quality of life in post-stroke patients [31]. Bale and Strand [32] reported that strength exercise performed based on the principle of 10–15 repetitions maximum resulted in significant gait speed improvements after strength training when compared to the control group.

Several studies have addressed the effects of strengthening exercise on gait performance (activity) and perceived participation (presented in Table 9.2). Park et al. [22] evaluated the effects of a progressive RE training program on walking ability in post-stroke patients and found that it can increase walking speed and decrease a 10-m walking time. Clark et al. [37] studied a dynamic high-intensity resistance training program over 5 weeks followed by 3 weeks of a clinic-based gait training and found that bilateral neuromuscular activation, strength, and walking speed improved in post-stroke patients. Lower limb training for 10–12 weeks can increase gait speed, and quality of life according to the Duncan et al. [34] and Flansbjer et al. [36] studies.

Fitness and mobility exercises can also increase gait distance in post-stroke patients [35]. Rodrigo et al. [38] performed closed-chain knee extensions in post-stroke patients and found a significant improvement in balance function and gait performance for these study participants. However, resistance training should involve monitoring the patient's heart rate, blood pressure, and subjective feelings.

2.3 Improve Functional Outcomes

A systematic review [40] reported that post-stroke strength exercise can result in an improvement of functional activity and quality of life measured by self-assessment scales such as the Short-Form 36 (SF-36), Maximal Activity Score (MAS), Nottingham Health Profile (NHP), Human Activity Profile (HAP), or the Barthel Index. Michelle et al. [41] found that a high-intensity progressive resistance training (3 sets of 8–10 repetitions, 3 times per week for 12 weeks at 70% 1RM) induced an improvement in self-reported function and disability. In addition, a single-blinded RCT [42] of 36-sessions over 12-weeks in a home-based exercise program that targeted strength (active motion in PNF unilateral patterns with manual resistance progressing to Thera band repetitions in 2 sets of 10) showed an improvement in physical and social aspects.

Table 9.2 Effects of strengthening exercise on gait performance and perceived participation

Study	Design	Intervention	Effects on gait performance
Bourbonnais 2002 [33]	RCT	Lower limb hip and knee (40–90%)	Sign between group differ for gait speed but not for TUGT
Duncan 2003 [34]	RCT	Manual resistance and terraband 10 reps, 2 sets, 90 min sessions, 12 w	Gait speed increased 26%, more significantly in intervention group
Pang 2005 [35]	RCT	Fitness and mobility exercise; intensity and duration increased as tolerated during the trial, 1 h, 3 days/week, 19 weeks	Significant difference for gait distance
Flansbjer 2008 [36]	RCT	PRT knee ext/flex both lower limbs, 2 sets, 6–8 reps 2 days/w, 10 w	Gait performance improved in both group. After intervention, there is significantly different in intervention group in follow up.
David 2013 [37]	RCT	Using an isokinetic dynamometer. 3 sets of 10 repetitions at each of 3 criterion speeds. 3 times weekly. 5 weeks of dynamic high-intensity resistance training followed by 3 weeks of clinic-based gait training	Improve bilateral neuromuscular activation, strength, and walking speed
SungMin 2014 [23]	RCT	3 sets (8–10 repetitions per set) of resistance exercise at 70% of the 1-repetition maximum (1RM) to strengthen muscles across multiple joints. 5 days per week, for a period of 6 weeks	Improve antero-posterior (A-P) and medio-lateral (M-L) sway distances, and TUGT times decreasing
Byoung 2015 [22]	RCT	Resistance weight was progressively increased from 30 to 40 kg and then to 50 kg. 3 sets of 11 presses and extensions for each weight increment. 30 min per time. 3 days/weeks for the 6 weeks	Increase walking speed and affected side stride length. Decrease 10-m walking time
Jennifer, 2016 [38]	RCT	POWER training, 40% 1 RM; 24 sessions; 8–12 repetitions	increases gait speed
Rodrigo 2016 [39]	RCT	4 sets of 7 maximal closed-chain knee extensions; <2 min of contractile activity per session; 12 weeks, 2 times/week	Enhance balance (8.9%), gait performance (10.6%), dual-task performance

2.4 Other Exercise Benefit Aspects

Other strength exercise benefits include an improvement in respiratory function, cognitive function, and anxiety. Song and Park [43] found that respiratory function (FVC, FEV1) and trunk control ability significantly improved after the exercise intervention (an chest resistance exercise program in moderate intensity supervised

by therapist, 30 min/time, 5 times/week for 8 weeks) in stroke patients. Marzolini et al. [44] found that resistance training (once per week for 6 months, 50% or greater 1 RM, and/or a resistance rated as 13–14 on the Rating of Perceived Exertion Scale, gradually progressed from 10 to 15 repetitions and then increased the resistance by 1.6–5 kg or increased the exercise band level) helped to improve mild cognitive impairment following stroke. A pilot study [45] indicated that resistance exercise (3 sets of 8–10 repetitions with the same intensity, in accordance with the values of the OMNI Scale, 45–60 min at a time, 3 times per week for 12 weeks) improved anxiety in those who had experienced an ischemic stroke.

3 Benefits of Flexibility Exercise

About 65% of all stroke patients have suffered spasticity, which may result in functional limitation because of muscle tightness and joint stiffness. Spasticity can also impair motor function. Evidence now suggests that flexibility exercises may benefit stroke survivors. The goal of a flexibility program is to relieve spasticity, improve motor function, range of motion, and prevent contractures. Stretch training involve basic management techniques, which include flexibility exercises and joint movements by their ranges of motion (ROM) through an external force [46, 47]. It is suggested that stretch training can prevent joint contracture and muscle spasticity [48], relieve spasticity [47, 49], decrease joint stiffness [46, 50] and improve functional activity [46].

3.1 Increase ROM

Joint range of motion is also improved transiently after flexibility exercises, chronically after about 3 or 4 weeks of regular stretching at a frequency of at least 2–3 times per week [51–56]. These flexibility exercises may improve the patient in as few as 10 sessions with an intensive program [57]. When flexibility exercise is used for warm-up training or combined with resistance training and aerobic training, it can help stroke patients increase their ROM. In Hyun-Ju Jeon et al. study, patients with post-stroke hemiparesis were assigned randomly to the experimental or control group. Changes in ROM was then measured in the experimental and control groups of the Monkey Chair and Band program at weeks 0, 4, 8, and 12. Significant differences were found in shoulder flexion at baseline and weeks. The experimental group showed a remarkable increase in ROM over time. In the control group, however, there were no remarkable improvements in ROM [58]. In another trial, stroke patients prescribed a ROM and flexibility routine carried out in class and home combined with resistance training or aerobic training of 90 min per day for 6 months reported a remarkable increase in joint ROM [59].

3.2 Prevent Contractures

Spasticity problems after a stroke can lead to muscle weakness and soft tissue contracture, pain, and spasticity appear within 1 week and contracture can occur within 2 weeks after a stroke [60, 61]. Data suggests that stretch training can effectively improve spasticity and motor function in post-stroke subjects with severe spasticity and weakness. Fan Gao et al. used an ankle stretching device with stroke patients, which included 12 sessions in sequence that each lasted 5 min with a 30 s break in between. Around 120 stretching cycles occurred, which lasted about 1 h. Stroke survivors had a significantly higher resistance torque and joint stiffness than the healthy controls before an intervention. After repeated stretching, Fan Gao et al. found that stroke survivors had a significant reduction in ankle joint stiffness and resistance torques [62]. In a randomized, controlled study of 21 stroke patients, a wrist-hand stretching device was used for stretching exercises, which were performed with three different weight bearing positions for 14 min. The 4-weeks stretching program was conducted in 3 sessions per day for 6 days per week in the patient's own home or office. A significant improvement in spasticity severity and motor function was observed [63]. In another study, a static stretching device was used on stroke patients, the exercise lasted 10 min per session and was performed every day for 2 sessions per day for 4 weeks. Findings showed that the static stretching device effectively improved spasticity and motor function in post-stroke patients with severe spasticity and weakness [64].

3.3 Increase ADLs

Stroke disability may lifelong and can limit an individual's independence and activities of daily living (ADL) [65]. The studies conducted on home-based exercise suggest that it can effectively improve mobility in post-stroke patients [66]. In a randomized controlled pilot study, 72 individuals with subacute ischemic stroke were instructed to start an exercise program. The exercise program combined flexibility and resistance exercises. Each exercise session lasted 1 h and occurred twice per week for 12 weeks. In this home-based exercise program, gains were observed in ADL and mobility [67].

In conclusion, flexibility exercise programs that combine resistance training or aerobic training can remarkably improve range of motion (ROM) in stroke patients. Flexibility exercises are an effective method to improve spasticity, motor function, increase ADLs, and prevent contractures.

4 Benefits of Neuromuscular Exercise

Recent studies have indicated that gait impairments usually persist after stroke, such as walking slowly and spatial-temporal asymmetry The ability to adapt a gait pattern is required to walk safely in the community [68]. Such phenomenon creates

numerous needs on the neural processes included in the control of medial-lateral (ML) stability. Due to the importance of turning in daily mobility [69], and the increased risk of falls and damages when turning [70], it is essential that post-stroke patients learn neuromuscular exercises to improve his or her ADL safety level through coordination and balance activities.

4.1 Promote Mobility

Beyond the promotion on the balance capability, perturbation training benefits the stroke patients' independent mobility. In a randomized controlled trial [71], participants who suffered a stroke were assigned to one of two groups: the perturbation training group and the traditional balance training group. Both manual perturbations (e.g., a push or pull from a physiotherapist) and rapid voluntary movements to cause a loss of balance. Perturbation training occurred twice per week for 6 weeks. With 1 year falls monitoring period and the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) and the Subjective Index of Physical and Social Outcome (SIPSO) to conform the risk of falls and physical activity and participation, we found that the occurrence of falls and activity limitations among post-stroke participants had been reduced. In addition, the functional balance and mobility had improved in the perturbation training group.

4.2 Improve Trunk Control

Another neuromuscular treatment that harnesses weight-shifting training (WST) on a precarious surface can produce significant effects on trunk stability, proprioception, and balance in participants with chronic hemiparetic stroke. One of main problems following a stroke is trunk instability. Eighteen participants were recruited and allocated to either WST or a control group in an observer-blinded and a pilot randomized controlled study [72]. The WST group included a weight-shift training program for 30 min and then a traditional exercise program for 30 min, while the control group received traditional exercise program for 60 min, 5 times a week for 4 weeks for both groups. Three outcome measures were used: trunk reposition error (TRE) to the target angle during his/her active trunk movement, trunk impairment scale (TIS) to measure trunk control abilities, and TUGT to measure dynamic balance abilities. After training, the TRE, TIS and TUG test scores showed a significant improvement in the WST group compared to the control group. These findings suggest that weight-shift training contributes to an improvement in trunk control and proprioception in individuals who have experienced a chronic hemiparetic stroke.

4.3 Improve Balance

Virtual reality training (VRT) allows post-stroke patients to interact with a virtual environment using computer software and hardware and can promote balance ability. In a randomized test control group design [73] that involved 22 stroke patients, the patients were divided into a video-game system (VRBT) group to use virtual-reality balance training and the others were in a control group. Both groups were provided a rehabilitation training program (physical and occupational therapy) for 60 min a day, 5 times a week for 6 weeks. The VRBT group took part in VRBT for 30 min a day, 3 times a week for 6 weeks. Dynamic balance ability was evaluated with the BBS while balance and mobility in balance was measured by a TUGT. Compared with the control group, there was a greater improvement on BBS and TUGT in the VRBT group.

Balance ability disorders not only impair daily functional activity, but also limit both physical and social activity. The normalization and/or restoration of the impaired balance function after a stroke has. Promoted efforts for effective balance training [74]. It appears based on our review that video game therapy and balance training can help individuals who have suffered from a stroke to regain their balance and reduce their fall risk.

5 Benefits of Traditional Chinese Exercise

Traditional Chinese exercises, which can include Tai chi, Baduanjin, Yijinjing, and Liuzijue involves a theory of mental and physical exercise. It is a self-methodology which was created by ancient Chinese. Traditional Chinese exercises are suitable for elderly people because it is easy to learn, low cost, highly safe, and provides an appropriate level of aerobic exercise. Due to the combination of physical movements with mental focus and relaxation [75, 76], traditional Chinese exercise offers additional benefits to traditional stroke rehabilitation. Some research states that traditional Chinese exercises can improve the ability of walking and balance and enhance muscle strength to improve motor system function [77, 78].

Tai chi is a popular exercise method among the elderly and is a traditional Chinese exercise, especially in Asia. It is considered a complex, multicomponent intervention that involves physical, psychosocial, spiritual, emotional, and behavioral elements [79]. As an exercise for promoting health, Tai chi has been practiced for hundreds of years in China and is gradually becoming accepted in Western countries. A systematic review indicated that intensive Tai chi exercise had some favorable effects on improving general cardiorespiratory fitness and functional status. In addition, Tai chi was potentially beneficial for cardiovascular disease in the elderly population, including stroke patients [80].

5.1 Improve Balance and Gait

Kim H et al. [81] found that the Tai chi experimental group (60 min at a time, twice weekly which consisted of 10 different movements for 6 weeks) demonstrated a statistically significant difference in the functional reach test and the dynamic gait index (which were used to evaluate dynamic balance). The experimental group demonstrated a statistically significant difference in both sway length and sway velocity. The average changes in the 10-min walk test and timed up and go test (which were used to measure gait ability) after treatment were statistically greater in the treatment group. Another study that [82] involved 80 post-stroke hemiplegia patients with balance impairment found that the BBS scores in the Tai chi pile work group was higher than those in the rehabilitation group after 12 weeks of training.

5.2 Reduce Risk of Falls

A randomized controlled trial [83] conducted by Piliae RE et al. suggested that a 1-h class 3 times weekly of Yang style 24-posture short-form Tai chi over 12 weeks (the most common style) reduced fall rates compared to post-stroke patients who practiced strength exercise, range of movement training, or routine care interventions. Tai chi subjects had two thirds fewer falls (5 falls) compared to those who practiced strength exercise and range of movement training (14 falls) and routine care (15 falls) groups. In addition, they concluded that Tai chi, strength exercise and range of movement training result in an improved aerobic endurance, and are suitable for community-based programs to help with stroke recovery and community reintegration.

5.3 Improve Quality of Life

In one study [84] of 18 first-stroke survivors, study group patients had to perform a 1 h twice per week for 12 weeks Tai chi exercise). They showed an improvement in the Duke Health Profile (a health status self-reported evaluate as four dimensions: symptom status and physical, social as well as emotional function such as general functioning and social functioning. In a Kim H et al. [81] study, the differences in the quality of life on the basis of the SF-36 scores for physical functioning, physical pain, ordinary health, vitality, and mental health classifications were significant for study group.

5.4 *Effects on Depression*

A study [85] that involved 68 post-stroke patients found that the experimental group (exercised 30 min at a time, twice per week, for 5 weeks with Tai chi which consisted of 10 different movements) demonstrated a statistically significant difference in Hamilton Depression Rating Scale scores. Therefore, the effects of setting Tai chi exercise were better than normal limbs exercise improving depression of patients after stroke.

Traditional Chinese training has an important role in improving physical function in post-stroke patients. However, there are some possible adverse events that may occur in this population including muscle problems, hypotension, and dizziness. A few people may report back, leg, or knee pain and there is an increased risk of an ankle sprain. Therefore, when we choose Chinese exercise for the rehabilitation of stroke patients, we should consider possible problems and use it properly.

6 Summary

Evidence strongly proves a positive role for physical training that involves exercise such as aerobic exercises, strength training (particularly involving the upper body), flexibility exercises, neuromuscular exercises, and/or traditional Chinese exercises for stroke survivors. Studies report that stroke patients can improve physiologically, psychologically, as well as their sensorimotor, strength, endurance, and functional influences from post-stroke training. Although more validation by randomized clinical trials and other properly designed studies are needed, this overview shows that stroke survivors should take part in a routine exercise during their post-stroke rehabilitation period.

Exercise training is a beneficial yet underused part of post-stroke care. The care and exercise that are provided to the patient after the stroke should contain exercise training suggestions to improve their overall health. These interventions may reduce the risk of future cardiovascular events such as another stroke and/or a myocardial infarction.

When studying the process of movement, we should always monitor various safety indicators of stroke patients. If any danger occurs, the test should be terminated immediately. Contraindications to exercise therapy of stroke include the following:

- Sustained blood pressure (BP) >185/110 Hg despite treatment;
- Platelet counts <100,000; hematocrit (HCT) <25%; glucose level < 50 or >400 mg/dL;
- Use of heparin within 48 h, a prolonged PTT, or an elevated INR;
- Rapidly improving symptoms;
- Prior stroke or head injury within 3 months;
- Prior intracranial hemorrhage;

- Major surgery in preceding 14 days;
- Minor stroke symptoms;
- Gastrointestinal bleeding in preceding 21 days;
- Recent myocardial infarction;
- Coma or stupor

With education and encouragement regarding the benefits of physical training after stroke and the development of suitable stroke programs in hospitals and communities, the ability to recruit individuals to post-stroke rehabilitation programs should improve. These programs, formulated by trained exercise professionals, should be supplied early after stroke, and should continue to be watched throughout to study their lifestyle-changing behaviors and effects on overall health.

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Chapter 10
Evidence on Exercise Training in Pulmonary Hypertension

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Abstract Pulmonary hypertension (PH) is a chronic, debilitating condition which gravely affects exercise tolerance and quality of life. Though most therapies focus purely on medical intervention, there is a growing body of evidence to suggest the role and benefits of exercise training. This chapter discusses the various physiological basis for exercise intolerance observed in PH and highlights the rationale for exercise training. Recent evidence related to exercise training is summarized and potential pathways to suggest adaptations to exercise training are put forward. While keeping the paper applicable to clinicians, details on evaluating exercise intolerance, prescribing exercise and setting up rehabilitation centers for PH are discussed.

Keywords Exercise • Cardiopulmonary exercise testing • Pulmonary arterial hypertension • Rehabilitation

1 Introduction

Pulmonary hypertension (PH) is a condition that is gaining global attention with the rise in prevalence, thanks to the rise in other diseases such as heart failure (HF) and chronic obstructive pulmonary disease (COPD) [1]. The recent World Symposium on Pulmonary Hypertension at France, has classified PH into five distinct etiological

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groups which are clinically relevant [2]. However, based on haemodynamic parameters, PH can also be classified as pre-capillary, post-capillary, isolated post-capillary and combined post- and pre-capillary PH [3, 4]. The changes in haemodynamics are related to pulmonary vascular remodeling which occurs due to a dysfunction of the pulmonary endothelial cells and vascular smooth muscles [5]. All these changes result in gross limitation to perform exercise as a result of various physiological mechanisms causing symptoms of dyspnea, fatigue and syncope [6–8].

Current therapies have focused on targeting the three main pathways of pulmonary vascular remodeling (i.e., endothelin pathway, nitric oxide pathway and prostacyclin pathway) through either sequential combination therapy or through an initial double or triple combination therapy [9]. With these advancements in medical therapies, survival years have only improved which have resulted in greater survivors of PH having poor functional capacity and quality of life [10, 11]. Thus, there is a need to work towards improving their function and quality of life through various rehabilitative interventions such as exercise training.

This chapter will focus on the various physiological mechanisms limiting exercise performance, the rationale for exercise training, evaluation of exercise capacity and an updated review of recent literature on exercise training in PH. In addition, key information on setting up a PH rehabilitation center will also be described.

2 Exercise Limitations in Pulmonary Hypertension

Exercise intolerance is a major finding across all forms of PH. A complex interaction between the pulmonary, cardiovascular and musculoskeletal systems are responsible for exercise intolerance seen in PH. Early studies by Sun et al., identified various central and peripheral mechanisms in idiopathic PH from cardiopulmonary exercise testing (CPX) [12]. A recent review, described the various limiting factors for various etiologies of PH and postulated possible mechanisms through which the various systems involving the right and left ventricles, pulmonary circulation, respiratory system and skeletal muscles all contribute to poor exercise tolerance in PH [6].

2.1 Haemodynamics and Exercise Limitation

Altered haemodynamics in the pulmonary circulation is a key finding in PH. Changes in pulmonary vascular resistance (PVR) and pulmonary artery pressures (PAP) under normal circumstances, allow for adequate decrease and maintenance to ensure homeostasis within the pulmonary circulation [7]. In a normal healthy individual, the response to exercise causes a drop in PVR secondary to recruitment of the vascular bed. In addition, minimal alteration in the radius of the vessel results in an almost fourfold increase in PVR [7]. These are similar to changes in pulmonary vascular distensibility in which a 2% per mmHg decrease of mean PAP occurs during high cardiac output [13]. However, changes in distensibility by even a meager 0.1% per mmHg, greatly increases the mean PAP resulting in a limitation of exercise. The

impact of the raised PVR is felt on the right ventricle (RV) and this results in uncoupling of the RV and the pulmonary vasculature [14]. A recent study further identified altered resting ventriculo-arterial coupling ratio which failed to increase during exercise thereby advancing the RV dysfunction and limiting exercise [15].

The altered size of the RV in turn compresses the left ventricle (LV) which subsequently affects CO by affecting the distensibility of the LV [16, 17]. This cycle continues with the progression of the uncoupling and consequently affects the RV contractile reserve [18]. In conditions like HF with reduced ejection fraction (HFrEF), there is a gradual increase in PAP due to the prolonged elevation of the PCWP [19]. HF with preserved ejection fraction (HFpEF), however, increases in left atrial pressure leads to remodeling and a decrease in compliance of the pulmonary arterial bed, thereby increasing the oscillatory load on the RV [20].

2.2 Cardiorespiratory Function and Exercise Limitation

Cardiorespiratory function as evaluated from cardiopulmonary exercise testing (CPX), which has now received a Level B, Class IIa recommendation for diagnostic evaluation [21], was initially used to describe two potential pathways resulting in exercise intolerance in PAH, i.e., an increase in ventilatory demand and impaired muscle contraction (which will be described in Sect. 2.3) [12].

These changes are more profound in chronic lung disease and chronic thromboembolic PH (i.e., Group 3 and group 4). Altered diffusion in chronic lung disease occurs as the result of altered biomechanics of the thorax and the hypoxia induced vasoconstriction causing the raised PVR [22] [23]. In addition, CTEPH, as a result of increased dead space ventilation, shows an abnormal decrease in end tidal carbon dioxide ($P_{ET}CO_2$) and abnormal rise in the minute ventilation – carbon dioxide production (V_E/VCO_2) relationship [24]. This has also been observed in other forms of PH like idiopathic PH, PH due to congenital heart disease and connective tissue disorders [25].

2.3 Muscles and Exercise Limitation

In addition to the altered pulmonary haemodynamics and cardiorespiratory system, muscle dysfunctions (both peripheral and respiratory) further contribute to exercise limitations. Poor oxygen delivery at the periphery due to circulatory changes result in lactic acid build up which has been shown to limit exercise [26]. In addition, limited cardiac output could result in overactivation of the sympathetic systems similar to that seen in HF [27]. Both these factors could contribute to the "generalized myopathy" observed [28]. The involvement of the diaphragm, along with the peripheral muscles, has been shown to further contribute to the exercise limitations seen in PH [29]. Changes in respiratory muscle strength have recently been shown to moderately strong relationships with functional capacity (r = 0.40) and physical activity (r = 0,38–0.61 for vigorous and moderate physical activity respectively) [30].

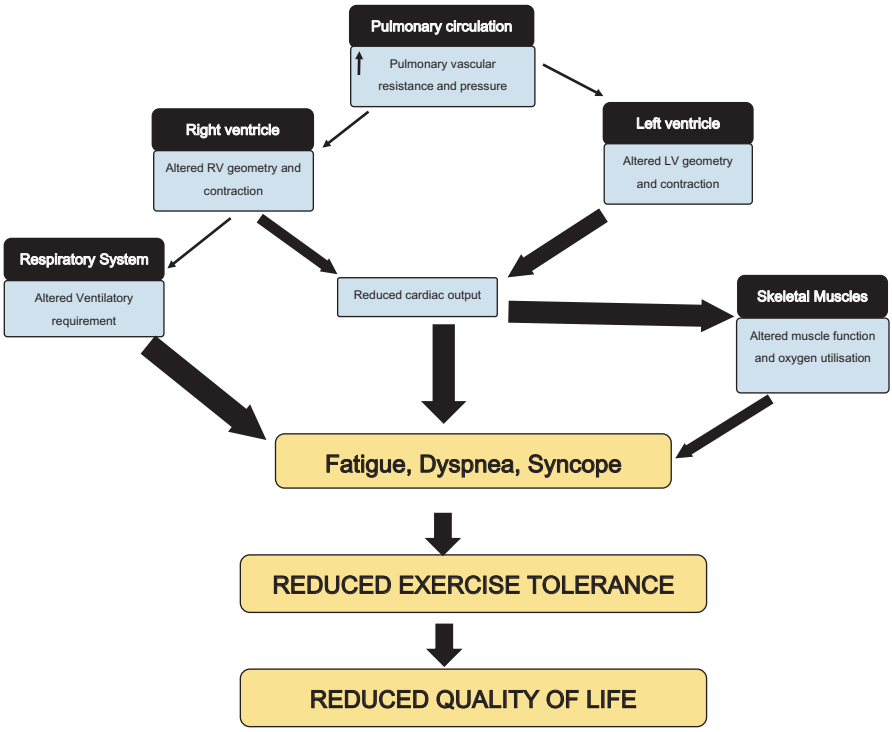

Fig. 10.1 Summary of mechanisms contributing to exercise limitations in pulmonary hypertension

Thus, the contributions of the various systems to exercise limitations in PH are summarized. Figure 10.1 provides a pictorial representation of the complex interplay of the various physiological systems.

3 Rationale for Exercise Training

Exercise training has been found to have numerous benefits on the cardiovascular system [31, 32] and skeletal muscle systems. Patients with HF and COPD have been shown to respond favorably to exercise training with marked improvements in exercise capacity, quality of life and longevity [33]. There exists similarity between limitation to exercise performance in both PH and HF. Both conditions have contributions from central factors, vascular function, respiratory system and peripheral muscles [6, 34]. Studies in HF have suggested potential mechanisms for improvements from the changes in the neurohumoral systems, endothelial function, anti-inflammatory effects, cardiovascular effects and skeletal muscle changes [35]. Considering these effects observed in HF, it is only logical to assume that these

same effects in a patient with PH would no doubt improve outcomes with exercise training. Indeed it was the anti-oxidant effects and improved vascular function of studies in HF that drove the hypothesis for exercise training in PH [36].

Since the publication of the first randomized controlled trial of exercise training study in humans [36], studies have continued to demonstrate significant benefits with exercise training on cardiorespiratory fitness (peak $\dot{V}O_2$), functional capacity (6 min walk distance-6MWD) and peripheral and respiratory muscle function in individuals with PH. In the first review on this topic Desai and Channick (2008) highlighted the rationale for exercise training in 2008 [37]. These authors also hypothesized the benefits of exercise in chronic obstructive pulmonary disease (COPD) and their mechanisms as potential reasons to advocate exercise training. Since then, the recent systematic reviews of the existing literature have supported the benefits of exercise training on various functional outcomes [38–40]. Thus, it appears that exercise training through various mechanisms, which still need to be elucidated, have an impact on clinical and functional outcomes in PH.

4 Evidence on Exercise Training in Pulmonary Hypertension

Evidence on the effects of exercise training in PH were limited till early 2000. However, there has been a steady increase in the number of trails registered in various clinical trial registries across the world [41]. Recently, there have been excellent reviews and meta-analysis on this topic and each one has focused on various aspects [38–40]. Moreover, the results of a Cochrane review on randomized controlled trials, has also recently been published [42].

This section compiles information from all these reviews and further contributes to articles available since the publication of these reviews. Among these three recent reviews, only one has included all forms of study designs [40] while the other two have focused only on randomized controlled trials [38, 39]. From the 15 trials included in the systematic review, there have been an additional four articles that have been published since the last search performed in the review [43–46], thus making a total of 19 observational and randomized controlled trial of exercise training published till date. A summary of these studies are included in Table 10.1.

As observed, most of the studies have observed changes in functional capacity and quality of life. Recent meta-analysis and systematic reviews have reiterated the benefits seen with regard to exercise capacity, functional class and quality of life [38–40, 47]. At present, conclusions from the randomized clinical trials [36, 44, 45, 48–50] suggest significant benefits in terms of exercise capacity (peak $\dot{V}O_2$), 6 min walk distance (6MWD), right ventricular systolic pressure (RVSP), mean PAP, PVR and quality of life. In addition to these studies, a recent paper assessed the use of home based exercises in children with PH [51]. However, in spite of the growing literature, the evidence base for exercise training remains narrow and the quality of the evidence remains low [42]. Furthermore, much of our evidence comes from the same group of authors that used an inpatient training program followed by a home based program.

Table 10.1 Summary of the various studies included in the review

Reference	N	Design	NYHA grade at enrolment	PH cause	Intervention (Intensity)	Duration	Results
[36]	30	RCT	II – IV	CTEPH, PAH	Exercise + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	85 m increase after 3 weeks and 96 m after 15 weeks for 6MWD ($p < 0.001$)
							Improved QoL in physical function and vitality ($p < 0.005$)
[62]	2	Case report		iPH and PAH due to scleroderma	Cycle ergometry (50% peak workload)	6 weeks – Institution based, 3 days/week	4% and 14% increase in peak VO2
							Improved QoL
[65]	19	Pre-post	II – III	iPH	Cycling and quadriceps muscle training while maintaining SpO2 > 85% and HR <120 bpm	12 weeks – Outpatient based	4% increase in 6MWD ($p = 0.13$)
							Increase in workload of AT from 32 to 46 watt; ($p = 0.003$)
							13% and 34% increase in quadriceps endurance and strength ($p < 0.05$)
[85]	8	Non-randomized controlled trial	II – III	Congenital heart disease	Interval training on bicycle and resistance training	2 days a week for 12 weeks – Outpatient? Based	No significant change in 6MWD and QoL
[63]	5	Case series	II – III	iPH	Aerobic and resisted exercises (60% max workload and 70% MVC)	12 weeks – Outpatient based	58 m improvement in 6MWD ($p = 0.01$)

[64]	22	Non-randomized controlled trial	II – III	iPH and CTEPH	Aerobic and resisted exercises + stair climbing (60–80% HRmax)	12 weeks – Outpatient and home based	32 m and 1.1 ml/kg/min improvement in 6MWD and peak VO2 ($p < 0.05$)
[54]	58	Pre-post	II – IV	iPH	Aerobic and resistance training + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	87 m and 2.1 ml/kg/min improvement for 6MWD and peak VO_2 ($p < 0.001$)
							Improvement in all domains of SF36 ($p < 0.05$)
[56]	183	Pre-post	II – IV	PAH, CTEPH, PH due to lung and heart disease	Exercise + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	68 m increase after 3 weeks and 78 m after 15 weeks for 6MWD ($p < 0.001$)
							Improved QoL ($p < 0.05$)
[57]	21	Pre-post	II – IV	PAH due to CTD	Exercise + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	67 m increase after 3 weeks and by 71 m after 15 weeks for 6MWD ($p < 0.05$)
							Improved QoL ($p < 0.05$)

(continued)

Table 10.1 (continued)

Reference	N	Design	NYHA grade at enrolment	PH cause	Intervention (Intensity)	Duration	Results
[55]	35	Pre-post	II – IV	CTEPH	Exercise + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	61 m increase after 3 weeks and 71 m after 15 weeks for 6MWD
							1.9 ml/kg/min in peakVO2 after 15 weeks
							Improved QoL ($p < 0.05$)
							>20% reduction fot NT-proBNP at 3 weeks
							1,2 and 3 year survival rates of 97%, 94% and 86%

[48]	23	RCT	I – IV	PAH	Education versus exercise training	10 weeks outpatient	56 m increase in 6MWD with exercise training ($p = 0.002$)
							Improvements in both QoL measurements ($p < 0.05$)
[58]	20	Pre-post	II – IV	PAH due to CHD	Exercise + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	63 m increase after 3 weeks and 67 m increase after 15 weeks for 6MWD ($p < 0.001$)
							Increase in peak VO_2 from 8.3 L/min to 9.02 and 9.25 L/min at 3 and 15 weeks respectively Significant improvement only in bodily pain 100% survival at years 1 and 2. Transplantation free survival 100% and 93% at years 1 and 2

(continued)

Table 10.1 (continued)

Reference	N	Design	NYHA grade at enrolment	PH cause	Intervention (Intensity)	Duration	Results
[49]	20	RCT	II – III	PAH, CTD, CTEPH, portal hypertension	Exercise + respiratory muscle training	3 weeks Inpatient	91 m improvement in the experimental group in 6MWD ($p = 0.008$)
[50]	24	RCT	I – IV	PAH, CTD	Education versus exercise training	10 weeks This is the same study as Chan et al.	53 m increase in 6MWD ($p = 0.003$) with exercise training
							Improved fatigue scores
[61]	7	Case series	III – IV	PAH		3 weeks – Inpatient based and 12 weeks – Home based	92 m increase after 3 weeks and 81 m increase after 15 weeks for 6MWD ($p < 0.001$)
							Improved PImax by 1 kPa ($p = 0.086$), PEmax by 2.3 kPa ($p = 0.021$), SnPna by 1.3 kPa ($p = 0.025$) at 15 weeks
[43]	8	Case series	II – III	CTEPH	Endurance + strength training	12 weeks, home based	33 m improvement in 6MWD
							Improved QoL

[44]	29	RCT	II – III	iPAH, PAH due to CHD, CTD and RA	Inspiratory muscle training	6 weeks	50 m improvement in 6MWD
							Improved mental components on Nottingham health profile
							26 and 10 cmH_2O improvement in MIP and MEP
							Increased FEV1 (6%) and FVC (10%)
[45]	87	RCT	II – IV	PAH, CTEPH	Exercise + respiratory muscle training	3 weeks – Inpatient based and 12 weeks – Home based	41 m improvement on 6MWD
							3.1 ml/kg/min improvement
[46]	27	Non-radomized	II – III	PAH	Exercise + respiratory muscle training + slow breathing + psychological intervention	4 weeks	~32 m improvement on 6MWD

6MWD – Six minute walk distance, *6MWT* – Six minute walk test, *CHD* – Congenital heart disease, *CTD* – connective tissue disorder, *CTEPH* – Chronic thromboembolic pulmonary hypertension, *HR* – Heart rate, *HRmax* – Maximum heart rate, *iPH* – Idiopathic pulmonary hypertension, *MVC* – maximal voluntary contraction, *NR* – Not reported, *PAH* – Pulmonary artery hypertension, *PEmax* – Peak expiratory pressure, *PImax* – Peak inspiratory pressure, *QoL* – Quality of life, *SF36* – Medical outcomes survey short form 36, *RA* – Rheumatoid arthritis, *SF12* – Medical outcomes survey short form 12, *SnPna* – Sniff nasal pressure, *SpO_2* – Oxygen saturation, *peak VO_2* – Peak oxygen consumption

This highly supervised, expensive model of exercise training would be difficult to incorporate into most standard rehabilitation programs around the world [52, 53].

5 Adaptations to Exercise Training

With the evidence supporting the use of exercise training to improve functional capacity and quality of life in PH, there are certain adaptations that could occur as a result of the exercise training programs. Most of the studies have utilized a combination of aerobic and resistance training interventions [36, 45, 54–61] with only a few relying solely on aerobic [62–64], peripheral [65] and respiratory muscle strengthening [44] and home-based exercise training [43].

The effects reported from all the studies have reflected to a certain extent changes in the RV and muscle strength. Few have also reported haemodynamic changes. Single groups studies have not reported significant changes, though there is a minimal decrease by 2–4 mmHg in mPAP at rest when assessed by either echocardiography or right heart catheterisation [36, 45] while some have reported no change at all [43]. Recent meta-analysis have also reported changes in peak systolic pulmonary artery pressure with exercise training (−3.66 mm Hg; 95% CI: -5.45, −1.87; p = 0.694) [39]. Recently, an abstract presented at the recent American Thoracic Society conference (2016) found that supervised exercise training improve RV function (with respect to RV stroke volume and ejection fraction) when evaluated with cardiac MRI [66]. RV function determined from tricuspid annular plane systolic excursion (TAPSE) was also seen to improve from 23 ± 10 mm to 21 ± 3 mm in a single group observational study. This is the only study till date to report improvements in TAPSE following exercise training [46]. Another cardiac MRI study also identified that 3 weeks of exercise training produced a reduction pulmonary artery flow resistance along with an increase in pulmonary perfusion [49]. Figure 10.2 summarizes the various adaptations reported from all the studied till date.

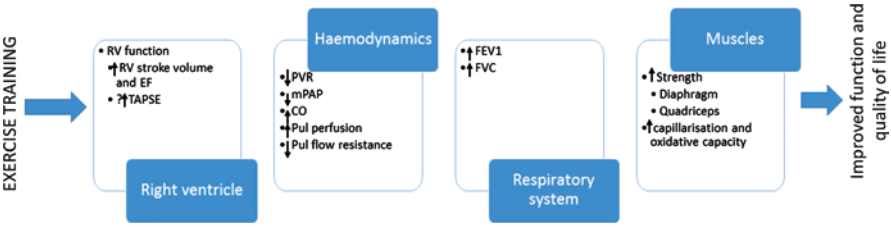

Fig. 10.2 Adaptations to exercise training programs in pulmonary hypertension form published literature

Abbreviations: *RV* – Right ventricle; *EF* – Ejection fraction; *TAPSE* – Tricuspid annulus planar systolic excursion; *PVR* – Pulmonary Vascular resistance; *mPAP* – mean pulmonary artery pressure; *CO* – Cardiac output; *Pul* – Pulmonary; *FEV1* – Forced expiratory volume in 1st second; *FVC* – Forced vital capacity

6 Assessing and Prescribing Exercise in Pulmonary Hypertension

Assessment of exercise capacity in PH has always played an important role. All through the years, the 6 min walk test (6MWT) has been used extensively due to its ease of administration. The importance of evaluating exercise capacity with CPX and 6MWT has been reiterated in the recent ESC-ERS guidelines as well [3]. The use of CPX or other functional tests like the 6 min walk test (6MWT), shuttle walk test, functional walk test or bag and carry test are dependent on setting and expertise [67]. However, CPX and 6MWT are the most commonly used methods for evaluating exercise capacity.

6.1 Cardiopulmonary Exercise Testing

CPX is the gold standard for the evaluation of exercise capacity and currently receives evidence based recommendations for diagnosis, prognostication and evaluation of therapeutic efficacy [21]. CPX is a non-invasive method that estimates the expired ventilation and concentration of oxygen and carbon dioxide through a breath-by-breath gas analyser while the patient exercises on a bicycle or treadmill. Various outcomes like peak $\dot{V}O_2$, peak respiratory exchange ratio (RER), anaerobic/lactate threshold, ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$ slope), end tidal CO_2 ($P_{ET}CO_2$) and dead space to tidal volume ratio (Vd/Vt) [68, 69]. In addition to these variables, heart rate, blood pressure, oxygen saturation, Borg's rating of perceived exertion and symptoms are further determined during the test. For the evaluation of PH however, peak $\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$ slope, $P_{ET}CO_2$, anaerobic threshold and Vd/Vt are the primary variables of interest.

Many of these variables have also been shown to have prognostic importance [21, 67]. High $\dot{V}_E/\dot{V}CO_2$ slope (>45), low peak $\dot{V}O_2$ (<10 ml/kg/min) and low $P_{ET}CO_2$ (no value established as yet) were consistently seen to have poor prognosis in PH with level IIb recommendation for Level B evidence [21]. In addition, CPX has also been found to have a role in determining therapeutic efficacy having a IIb level of recommendation with Level C evidence. This may change in the current years, as to date, nearly all the existing PH research has relied very heavily on the popular 6 min walk test (6MWT).

As with standard exercise testing procedures, pre-testing screening and calibration of equipment is important. Adequate infrastructure and space for the exercise testing lab are crucial considering the amount of equipment that will need to be stored. Presence of emergency resuscitation equipment and personnel trained in both basic and/or advanced resuscitation need to be available. In addition, to life saving skills, competencies in ECG recording and interpretations are highly important [70]. Finally, the level of experience in the individuals is important for CPX testing, with more experienced centres showing greater reliability [71].

6.2 Six Minutes Walk Test

The 6MWT has been widely used in PH studies as a measure of functional outcome and has been used as recommended by the American Thoracic Society and European Respiratory Societies [72, 73]. The recent guidelines continue to emphasis the need for measurement of the 6MWD as an outcome for risk stratification [3]. The 6MWT has been used as an outcome measure in a number of clinical trials and the minimally important difference (MID) well characterized in the PH population [72, 74]. The 6MWT has been found to elicit a maximal cardiovascular response among patients with PH [75]. The test has been found to predict peak VO_2 in both children and adults with PH with varying levels of accuracy ($r = 0.87$; $p < 0.001$ and $r = 0.68$; $p < 0.001$ respectively) [76]. In adults however, ventilatory efficiency was found to be lower during the 6MWT with only a moderate correlation between 6MWD and peak VO_2 from CPX ($r = 0.49$) [75]. Yet, the worsening of 6MWD has been shown to be associated with poor prognosis, though improvements in 6MWD have not been found to be reflective of mortality benefits as yet [77]. However, this is now a topic of controversy as a recent study did not find any changes in 6MWD and between patients on monotherapy and triple therapy despite differences being observed in their VE/VCO_2 and $P_{ET}CO_2$ [25].

Despite the fair amount of inaccuracy of the 6MWT to predict peak VO_2, the fact that the test elicits a maximal cardiovascular response makes it an ideal alternative to test patients with PH [78]. This holds good in low resource settings where the cost for setting up a CPX lab can go higher than USD50000 [67].

The 6MWT though used frequently is not without any risks. There are a few studies that have reported adverse events with the 6MWT which further increases the need for close monitoring during the test [40, 79, 80]. The use of telemetric monitoring systems (where available) during the test or having the supervisor of the test walk behind the individual being tested could be an appropriate safeguard to this group of patients who can experience sudden arrhythmias resulting in cardiac arrest even during a sub-maximal test [72].

7 Setting Up a Pulmonary Hypertension Rehabilitation Center

Rehabilitation centers focusing on PH are limited. Currently, these patients are enrolled along with HF cardiac rehabilitation programs or pulmonary rehabilitation programs. However, there are no dedicated programs for PH per se. The Pulmonary Hypertension Association, USA has initiated a program to establish PH care centers (PHCC) across the various parts of the US (accessed from: http://www.phassociation.org/PHCareCenters). This program accredits centers with expertise in the evaluation and management of PH to improve outcomes of patients with PH [81]. The goal of these centers are to provide evidence based team care to patients with PH, improve access of specialized health care, promote adherence to guidelines to optimize research and clinical services, and promote awareness [82].

Development of centers for comprehensive care require expertise in staff and support services, facilitates and research. Despite these guidelines for PH specific centers, there is limited mention for the need of physiotherapists/exercise physiologists as part of the comprehensive healthcare team. Though referral to cardiac or pulmonary rehabilitation programs are described, this is not considered as a part of the center requirements. This section, expert driven, will provide a framework for the development of a PH rehabilitation center which has been developed and modified from both the cardiac and pulmonary rehabilitation programs (Tables 10.2 and 10.3).

The PH rehabilitation center working along with PH care centers or as a part of them can be developed on the model of both cardiac and pulmonary rehabilitation centers. Table 10.2 provides a list a staff, facilities and services that should be made available at a PH rehabilitation center. Though these are components that would be desirable to have, it should also be kept in mind that even the use of simple cost effective methods are acceptable. The recent model for and consensus statement on low cost cardiac rehabilitation could be used as a source to guide setting exercise training programs in low resource settings [83, 84] even for PH; though this will need to be evaluated 8.

Table 10.2 PH rehabilitation center: Staff, facilities and services

Staff
Physician with expertise in PH
PH nurse
Clinical pharmacist
Physiotherapist
Exercise physiologist
Occupational therapist
Nutritionist
Social worker
Psychologist/Psychiatrist
Facilities
Evaluation labs for assessment of pulmonary function, cardiorespiratory fitness, muscle strength (both peripheral and respiratory), autonomic function (heart rate variability), energy expenditure and body composition
Exercise training areas for aerobic, resistance and respiratory muscle training
Patient education rooms
Counselling areas
Areas of groups discussions and therapy
Work simulation labs
Services
Exercise training
Nutritional counselling
Vocational rehabilitation
Psychological support
Patient education

Table 10.3 Projected requirements for evaluations of patients with PH

Assessment	Team member performing	Baseline	Follow up
Electrocardiogram	Cardiologist	√	√
Echocardiography	Cardiologist	√	√
Right heart catheterisation	Cardiologist	√	
Pulmonary function test	Exercise physiologist/physiotherapist	√	
Diffusion capacity evaluations	Exercise physiologist/physiotherapist	√	
Exercise capacity			
CPX	Exercise physiologist/physiotherapist/physician	√	√
6MWT	Exercise physiologist/physiotherapist/nurse	√	√
Inspiratory muscle strength	Exercise physiologist/physiotherapist	√	
Peripheral muscle strength	Exercise physiologist/physiotherapist	√	
Quality of life	Nurse	√	√
Depression	Nurse/psychologist	√	√

8 Future Recommendations

The future for exercise in PH is bright. There is scope numerous avenues of research in this area. At present, greater good quality studies are required to further systematically assess the effects of exercise training through various models, intensities and modes on cardiovascular and haemodynamic outcomes. In addition, long term studies assessing time to clinical worsening and hard outcomes like mortality need to be addressed. If PH rehabilitation centers can be developed, they will offer valuable evidence through prospective databases and registries on the effects of exercise.

9 Conclusion

Exercise intolerance is a major hindrance to function and poor quality of life among patients with PH. Evaluation of the mechanisms of intolerance are important prior to initiation of rehabilitation. Cardiopulmonary exercise testing and the use of functional tests are useful in the assessment and prognosis of these patients. Exercise training interventions are showing promising results, however, there is a need for more generalizable results and feasible exercise training protocols for patients with PH. Nevertheless, exercise training will have an impact on the various physiological systems of the body and will result in numerous adaptations which will help improve function and quality of life (Table 10.3).

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Chapter 11
Peripheral Vascular Disease: The Beneficial Effect of Exercise in Peripheral Vascular Diseases Based on Clinical Trials

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Abstract Intermittent claudication (IC) due to peripheral artery diseases (PAD) is one of the disabling disease that can affect quality of life (QOL) and functional status of capacity. It is characterized by cramping pain which develops with exercise and eliminated by rest secondary to decrease blood flow to the muscles. The annual incidence rate is increased with age. Exercise rehabilitation has a great impact in improving the functional capacity and prevent the functional disability. The available evidences from current studies have showed that exercise therapy is considered the primary treatment in PAD, which in consequently improves the QOL. In this chapter we will illustrate the current available evidences which support exercise benefit and outcomes in PAD with IC.

Keywords Peripheral vascular disease • Exercise • Intermittent claudication

1 Introduction

Intermittent claudication (IC) or peripheral artery diseases (PAD) is a cramping pain which develops after or during exercise and is improved by rest. It is secondary to insufficient blood flow to the muscles. It is obvious that IC incidence increases with age. The annual incidence rate of IC is 0.7%, 3.9%, and 10.6% within 35–44 year-old men, 45–54 year-old men, and 55–64 year-old men, respectively, however the incidence decreases up to 50% lower in females [1]. Intermittent claudication prohibit patients' mobility, activity and lifestyle incapacitation [2, 3].

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Peripheral artery diseases decrease the functional capacity leading to disability [4, 5]. Exercise rehabilitation therapy associated with proper secondary prevention has the desirable effect to preserve and improve the functional capacity and reducing cardiovascular events.

According to the available evidences, exercise is considered the primary therapy in PAD. It improves the quality of life (QOL). There is rising evidence that Community-based supervised exercise has the potential to be as effective as programmed hospital exercise [6]. In this chapter we will address the available evidence of exercise benefit and rational in patients with IC and PAD, types of PAD associated exercise in randomized studies with selection to good evidence based trials with low risk of bias.

2 Beneficial Effects of Exercise on PAD

Impaired walking ability due to PAD has several important clinical, physical and social implications. PAD patients have markedly decrease in QOL and higher depression prevalence [7, 8]. Diminished physical activity can predict higher mortality rate in PAD [9]. These findings suggest exercise rehabilitation in patients with PAD associated with numerous benefits [10].

Exercise prescription in PAD is known to improve the adaptations. It is also one of the effective ways of management PAD patients without associated contraindications, however compliance is one of the crucial problem. Public education is needed to explain the importance of modifying patients' life style to encourage the compliance of the daily exercise activity [11].

Supervised exercise programs have been considered as first line PAD treatment [12–14]. Recent studies revealed beneficial effect of practicing exercise also in PAD patients without claudication pain [15]. Exercise training programs with standard risk factors modification improve the clinical outcome of PAD patients, which aim to improve limb symptoms and escalate exercise endurance to decrease physical disability, and limit the cardiovascular events.

Accordingly exercise rehabilitation has been highlighted in the current PAD management guidelines, including American Association of Cardiovascular and Pulmonary Rehabilitation 2004 Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs, American College of Cardiology/American Heart Association 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease, Intersociety Consensus for the Management of PAD (TASC II), and American College of Sports Medicine 2010 Guidelines for Exercise Testing and Prescription. They all recommend treatment of IC symptomatic PAD patients with supervised training exercise [13, 14, 16, 17].

2.1 Quality of Life and Exercise

PAD affects the QOL parameters especially the physical health domains as pain and discomfort, level of Independence, mobility energy, fatigue, and daily living activities, which indirectly leads to work deficits. Both treadmill and resistance exercise showed improvement in functional physical capacity and associated QOL measures [15].

Psychosocial impact of exercise and even on depression degree is also noted [18–20]. The improved tolerance of activity and exercise endurance induced by exercise has a cardinal effect on the QOL in PDA. So, exercise program will establish excellent advancement in the domains of QOL [21].

2.2 Exercise Improves Inflammatory/Haemostatic Function

There is an evidence of paradox in the circulating inflammatory markers and inflammatory status with exercise. It is well known that sudden sustained exercise can elevate some markers of inflammations, especially noticed in athletes free from health problems, but on the other way, it was documented that training with exercise program produce sustained anti-inflammatory markers for longer duration [22].

2.3 Enhancement of Walking Efficiency in PAD with Exercise

Exercise training programs markedly enhance the walking ability in PAD patients and IC. After training the PAD patients experience more lengthened efficient exercise. As patients' maximal oxygen consumption (~12%) is significantly increased with improvement in endurance time, with less profound muscle fatigue after training, which leads to a lesser further motor units recruitment as time prolonged, in turn it helps to keep the oxygen consumption stationary. Accordingly, exercise training programs can marvelously augment the muscle function bio-physiology reactions in PAD patients [11].

A performed meta-analysis study, which collected uncontrolled trials supported the efficacy of training exercise to lessen manifestations of IC, thus supervised exercise found to improve walking distance with low pain or pain free up to 180% [23]. Another 2008 systematic Cochrane review, included controlled trials only, with overall 22 trial including 1200 participants. They compared supervised training exercise programs to standard known clinical care in the treatment of IC [24], in which there was significant improvement regarding the walking time and distance in the exercise group. The difference in other studies results mainly attributed to the degree of exercise intensity and adherence to exercise programs, however the enormity of functional beneficial effect from exercise exceeds that with drug therapy trials [25].

A recent study speculated on therapeutic exercise impact to larger group of PAD patients free from IC manifestations. McDermott et al., has performed a randomized controlled study of usual care, compared to supervised treadmill exercise in 156 PAD patients. There were 18% patients had IC and 82% were asymptomatic or with atypical manifestations. Within 6 months follow up, the group of treadmill exercise experienced improvement in exercise insurance with more enhancement in 6 min walking distance in comparison to a detrimental response in the control group [15].

2.4 Endothelial-Mediated Vessel Dilation Effect

There is a notable decrease in Flow-mediated dilation FMD in chronic cardiovascular patients, which is an independent predictor factor of having more risk of coronary artery disease [26], as same as in PAD, decreases FMD is also considered as an independent predictor factor in patients with PAD [27].

The muscle activity can cause dilation of large conduit arteries and consequently reduces the resistance to allow optimum active muscle perfusion. Lacking of such mechanism could decrease the flow of blood to the working skeletal muscles. The dilatation of conduit arteries, FMD, is thought to be a reflection of endothelial vasodilatation, so regular programmed training exercise indirectly can increase conduit arteries' diameter, with increase in FMD [28].

2.5 Increased Capillarity with Training Exercise

Endurance-type exercise training is one of the active skeletal muscle training with adaptations induced by an increase the capillary number within the active muscle through angiogenesis [29–31]. Muscle capillarity improve the nutritional and blood flow within the active muscle and increase oxygen exchange with increasing the capillary surface area and muscle perfusion.

3 Exercise Rehabilitation Programs for PAD with Proven Beneficial Effect

3.1 Supervised Exercise Training Programs

In comparison between supervised and unsupervised exercise training programs showed a better outcome in functional status in supervised training group. A Cochrane review analysis in 2006 on 319 participants of 8 small randomized controlled studies speculated the superior effect of supervised training exercise over the unsupervised one, with improvement of both walking time and distance [32].

In the societal guidelines, the non-supervised exercise in PAD stated as low/limited evidence recommendation [13], however the overall beneficial effect of daily exercise activities associated with wide range health improvement [33]. This differences attributed to unsupervised exercise can be improved by proper patient education about the importance of exercise adherence and compliance.

Another important factor to support supervised exercise programs is the recording and evaluation of the baseline functional capacity, therefor the American Heart Association and the American College of Cardiology, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the American College of Sports Medicine, encourage treadmill exercise test as a baseline before starting exercise training program to pick up exercise limitation and contraindications secondary to coronary artery disease, and exercise induced cardiovascular ischemia and arrhythmias, with assessment of baseline walking capacity [13, 16, 17].

One of the important multicenter studies 'Claudication: Exercise Versus Endoluminal Revascularization'(CLEVER) trial [34], in which the 6 months follow up, with primary outcome of peak walking time (PWT), which improved in exercise group in comparison to revascularization group with only medical treatment (+5.8 vs. + 3.7 vs. + 1.2 min). However claudication onset time (COT) values improved in the supervised walking groups as well as revascularization patients with higher values in exercise group (+3.0 vs. + 3.6 vs. + 0.7 min) [35].

3.2 Community-Based Walking Exercise

A meta-analysis review of supervised and non-supervised exercise training programs reviled that supervised exercise therapy was superior over non-supervised regimens [24]. However, a 12 week study compared PAD patients for supervised and community exercise training programs without control group, with close exercise compliance monitoring, through exercise sessions documentation by dairies or log books. The exercise training program was intermittent walking for 3 days per week till maximal leg pain, however in community exercise group, patients walked and rested initially for 20 min over a 2 week with regular increase of duration by 5 min till total of 45 min of walking reached. Positive significant enhancement were shown for COT and Peak walking time (PWT) for both exercise training group, with results of (+165 and + 215 s, $P < 0.001$) in supervised exercise training group, however the community exercise group the result was (+134 and + 124 s, $P < 0.01$). Thus raise the evidence of the community exercise programs beneficial effect. This implement the importance of monitoring, and compliance for proper outcome [16, 17].

Exercise training programs is recommended to be life-long activity, especially till now; the value of home exercise in PAD patients need more studies to support the beneficial concept. A recent Dutch study that the supervised exercise training program was superior to non-supervised exercise training program but more costly for patients with PAD [36].

3.3 Ergometry

Tuner et al., evaluated the cardiorespiratory outcomes and absolute claudication time during incremental cycling and treadmill exercise testing. It was showed to have higher effective metabolic and cardiovascular response compared to treadmill walking [37]. Arm ergometry exercise was also found to increases walking performance in patients with PAD [38, 39]. Bronas et al., revealed a notable improvement in IC onset distance over 12 weeks follow up for patients with arm ergometer exercise program (+89.6 m, $P < 0.01$) as well as patients in a supervised program with walking (+106.7 m) also, there were no differences in maximum walking distances for patients in comparison to ergometer exercise program (+181.1 m) versus the supervised walking program group. These findings can provide evidence for the use of leg and arm ergometry as a valid approach for patients with PAD, however more longitudinal studies is needed to support this concept [40].

3.4 Pole Striding

Pole striding is a type of exercise where increasing the central cardiovascular demand of patients, by pole ambulation resulting in excessive motion thereby of the upper body. The results of the few studies testing the efficacy of this modality in PAD was promising for treating IC [41–45]. Collins et al. [45], studied the effect of pole striding therapy versus supervised walking exercise with the change over 24 weeks, in PWT of supervised walking group was superior but insignificant in comparison to the pole striding group, pole striding could be an alternative to standard walking programs, however large multicenter longitudinal trials are needed to confirm this concept.

3.5 Resistance Training

Resistance training is composed of alternative types of exercise, as plantar flexion with strength training of upper body or lower body endurance. Tebbutt et al. [46], is 12 week planter flexion randomized PAD patients (n = 42) plus advise to walk at home to an unsupervised intervention group and a control group with advise of home walking exercise. The result showed significant increase in peak walking distance and median claudication onset distance for PVD patients in the plantar flexion exercise which was insignificant in the control group. Unfortunately this study was discontinued prematurely, a considerable randomized studies is advised to detect the beneficial effect of plantar flexion exercise.

3.6 Systematic Review to Compare Modes of Exercise Training for PAD

One of the important Cochrane Database of Systematic Reviews who reviewed a total of 5 studies with a low bias risk, to compare supervised walking exercise and other different exercise modalities, as strength training, cycling, and ergometry of upper-arm. Total sample size was 135 patients. The result revealed non-significant difference between supervised walking exercise training and other different exercise modalities regarding maximum walking distance on a treadmill, and pain free walking distance. They concluded that no evidence or significant differences between supervised walking exercise training program and other different exercise modalities in enhancing the pain-free and maximum walking distance of patients with PAD, however more large number randomized controlled studies are advised [6].

4 Beneficial Effect of Exercise in Comparison to Standard Way of Management

Limited controlled randomized trials had compared percutaneous revascularization and supervised training exercise in PAD participant especially with aorto-iliac and femoro-popliteal PAD. It has been shown that supervised exercise or endovascular revascularization in PAD patients with IC showed similar beneficial effect in form of clinical improvement, better functional outcome, and QOL [47–49].

Treesak et al. [50] has studied the cost effect of supervised exercise training and endovascular therapy of 3–6 months in PAD patients who is symptomatic for IC. The Findings of endovascular therapy at 3 months was higher clinical improvement than exercise program especially regarding increase of the maximum walking distance, but the long-term outcomes at 6 months revealed that exercise program of training gains more in walking distance with lesser cost per meter estimated as $61 as or less than that in endovascular therapy. Another important single randomized trial, has showed that lower limb bypass surgery and both exercise training enhance the peak maximal walking distance over 1 year to same endovascular therapy degree [51].

The (CLEVER) or Claudication, Exercise versus Endoluminal Revascularization study is one of the important multi-center trial evidence that compare medical treatment, interventional stenting, and supervised exercise (SE) training in PAD patients with IC [52]. The results of CLEVER study showed improvement of peak walking time (PWT) over 8 months follow up for both SE group (5.0 ± 5.4 min) and stenting ST group (3.2 ± 4.7 min) statistically significant higher than optimal medical therapy (0.2 ± 2.1 min; $p < 0.001$ and $p = 0.04$, respectively). There was no statistical significant difference between exercise and stenting group. Clinical decrease in claudication onset was higher for SE compared with optimal medical therapy, which

was not for ST in comparison with optimal medical therapy. Numerous QOL scales demonstrated longstanding clinical betterment higher for ST compared with SE or optimal medical therapy. Their conclusion was that the outcome of both SE and ST was better over 18-month follow up than optimal medical therapy. SE and ST showed similar improvement outcome in functional capacity and in QOL.

In 2008 systematic review has been conducted by the Cochrane group, included 22 studies with overall 1200 participants. It has studied supervised exercise training in comparison to standard medical care for PAD treatment, with 2 weeks to 2 years Follow-up period. All advised at least 2 weekly sessions of the exercise regimens used. Quality of the reviewed trials was assessed and it was considered good, although most of these trials were small sample size. Fourteen trials has compared different exercise programs with slandered care or even placebo, resulting in, exercise training showed improvement of peak walking time, and the total walking ability enhancement, with improvement of walking distances. They concluded that exercise has produced significant clinical and functional effect exceeds the observed in trials of drug therapy [24].

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Part II
Molecular Mechanisms

Chapter 12
The IGF1-PI3K-Akt Signaling Pathway in Mediating Exercise-Induced Cardiac Hypertrophy and Protection

Kate L. Weeks, Bianca C. Bernardo, Jenny Y.Y. Ooi, Natalie L. Patterson, and Julie R. McMullen

Abstract Regular physical activity or exercise training can lead to heart enlargement known as cardiac hypertrophy. Cardiac hypertrophy is broadly defined as an increase in heart mass. In adults, cardiac hypertrophy is often considered a poor prognostic sign because it often progresses to heart failure. Heart enlargement in a setting of cardiac disease is referred to as pathological cardiac hypertrophy and is typically characterized by cell death and depressed cardiac function. By contrast, physiological cardiac hypertrophy, as occurs in response to chronic exercise training (i.e. the 'athlete's heart'), is associated with normal or enhanced cardiac function. The following chapter describes the morphologically distinct types of heart growth, and the key role of the insulin-like growth factor 1 (IGF1) – phosphoinositide 3-kinase (PI3K)-Akt signaling pathway in regulating exercise-induced physiological cardiac hypertrophy and cardiac protection. Finally we summarize therapeutic approaches that target the IGF1-PI3K-Akt signaling pathway which are showing promise in preclinical models of heart disease.

Keywords IGF1-PI3K-Akt signaling • Exercise • Heart

1 Introduction

In adults, heart enlargement, also known as cardiac hypertrophy, is usually considered a poor prognostic sign because it often progresses to heart failure. Consequently, there has been great interest in examining the molecular mechanisms responsible for the induction of cardiac hypertrophy and transition to heart failure. It is also recognized that not all forms of cardiac hypertrophy progress to failure. In response to regular exercise training, the heart enlarges, but this can protect the heart against

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cardiac disease and heart failure. This type of heart enlargement is typically referred to as physiological cardiac hypertrophy or the "athlete's heart". The following chapter describes the morphologically distinct types of heart growth, and the key role of the insulin-like growth factor 1 (IGF1)-phosphoinositide 3-kinase (PI3K)-Akt signaling pathway in regulating exercise-induced physiological cardiac hypertrophy and cardiac protection. Finally, we summarize therapeutic approaches that target the IGF1-PI3K-Akt signaling pathway which are showing promise in preclinical models of heart disease.

2 Cardiac Hypertrophy and the Association with Heart Failure Versus Cardiac Protection

Cardiac hypertrophy refers to an increase in heart mass. Enlargement of the adult heart is closely matched to its functional load [1]. Load will increase in conditions such as chronic high blood pressure or exercise, and this increased load forces the heart to work harder. The heart is able to counteract the increased load / wall stress via the synthesis and assembly of contractile proteins within cardiomyocytes. This results in an increase in cardiomyocyte size and cardiac hypertrophy [2–4]. Initially, the increase in heart size allows the heart to function normally at rest, and the heart enlargement is referred to as compensated cardiac hypertrophy. However, if the chronic increase in wall stress persists (as occurs in heart disease settings), the heart chambers will dilate, cardiac function falls and the heart ultimately fails (also referred to as decompensated hypertrophy and heart failure). Thus, cardiac hypertrophy is often considered a poor prognostic sign. Furthermore, cardiac hypertrophy is an independent risk factor for arrhythmia, myocardial infarction (MI) and sudden death [5–7]. A notable exception to the association of cardiac hypertrophy and heart failure is the athlete's heart. The heart enlarges in elite athletes in response to chronic exercise training but this does not progress to heart failure in the normal population. Furthermore, it is well recognized that regular exercise in humans is associated with reduced cardiovascular disease risk and all-cause mortality [8–11]. An understanding at the molecular level of why heart disease-induced cardiac enlargement progresses to heart failure but exercise-induced cardiac enlargement does not, is considered important for uncovering the mechanisms responsible for the transition to heart failure, as well as identifying new therapeutic targets.

2.1 Morphologically Distinct Forms of Cardiac Growth and Hypertrophy: Physiological Versus Pathological

Cardiac growth is typically classified as physiological or pathological (Fig. 12.1). The term physiological cardiac hypertrophy encompasses postnatal heart growth, pregnancy-induced hypertrophy and exercise-induced cardiac enlargement. By

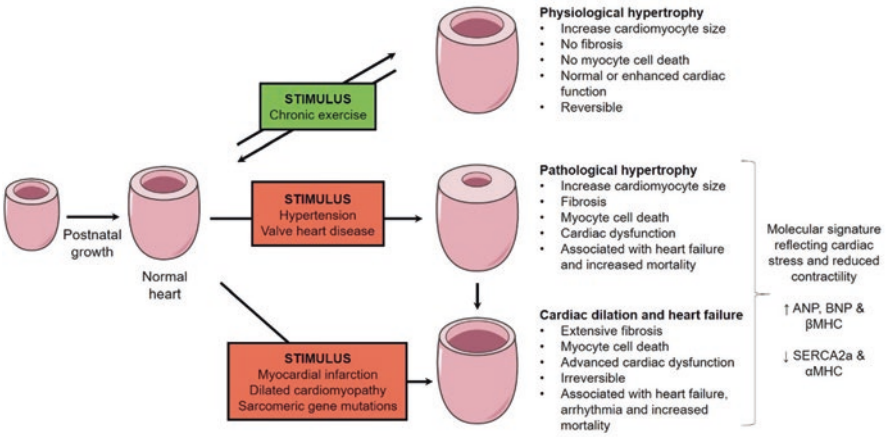

Fig. 12.1 Features of physiological and pathological heart growth, and the transition to heart failure

contrast, the term pathological growth has been used to describe heart growth in response to chronic pressure or volume overload under disease conditions (e.g. hypertension, valvular heart disease), MI or ischemia, inherited genetic mutations or diabetes.

The heart is composed of cardiomyocytes (specialized muscle cells composed of bundles of myofibrils that contain the basic contractile units of the heart: sarcomeres), non-myocytes (e.g. fibroblasts, endothelial cells, mast cells, vascular smooth muscle cells), and surrounding extracellular matrix [1]. In mammals, the majority of cardiomyocytes appear to lose their ability to proliferate at, or soon after, birth and growth occurs largely due to an increase in cardiomyocyte size [12]. Ventricular cardiomyocytes make up only one-third of the total heart cell number, but account for the majority of the heart's mass (70–80%, [1]). Both physiological and pathological stimuli lead to an increase in heart size, which appears to be largely due to an increase in cardiomyocyte size. Though, as described in Chap. 6, exercise is also reported to lead to the formation of new cardiomyocytes.

Animal studies have demonstrated that the mass of the heart can increase to a similar degree in response to pathological and physiological stimuli, e.g. 40% in response to aortic-banding or chronic swim training [13]. However, this is where the similarities generally end. It is well recognized that pathological and physiological cardiac hypertrophy are associated with distinct functional, histological and molecular profiles (Fig. 12.1) [14]. Pathological hypertrophy is typically associated with loss of myocytes and fibrotic replacement, inadequate angiogenesis, cardiac dysfunction, an increased risk of heart failure and sudden death [5, 15–17]. In contrast, physiological heart growth is associated with normal cardiac structure, maintained or enhanced heart function, and is typically reversible e.g. heart size returns to normal size with detraining or after pregnancy (Fig. 12.1) [18–20]. These distinct phenotypes are also associated with distinct molecular signatures. Pathological hypertrophy has been associated with upregulation of fetal genes, such as atrial- and

B-type natriuretic peptides (ANP, BNP) and β myosin heavy chain (β-MHC), and downregulation of genes important for maintaining contractile function, such as α-MHC and sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) [21–23]. By contrast, this pattern of gene expression does not commonly occur in models of exercise-induced physiological hypertrophy [13].

3 Cardiac Enlargement at the Cellular and Molecular Level

Significant insight regarding the cellular and molecular mechanisms responsible for the induction of pathological and physiological cardiac hypertrophy have been obtained by studying genetic mouse models. Since cardiomyocytes make up 70–80% of the heart's mass, investigators have focused on examining the role of signaling pathways in cardiomyocytes. However, numerous events/processes must occur in parallel with myocyte and heart growth for the maintenance of cardiac function. This includes vascular adaptations (e.g. angiogenesis), mitochondrial adaptations, and regulation of the extracellular matrix (described in Chaps. 14, 31, 35). In physiological settings (basal conditions or physiological cardiac hypertrophy), the fibrillar collagen network provides structural integrity for adjoining cardiomyocytes, allowing the heart to pump efficiently [24]. Pathological cardiac hypertrophy is typically associated with cell death that is replaced with an accumulation of excess collagen (fibrosis; stiffens the heart and impairs cardiac contraction) and inadequate angiogenesis [15, 17]. Fibrosis and reduced capillary density leads to myocardial ischemia and is likely to contribute to the transition from pathological hypertrophy to failure [24].

3.1 Hypertrophic Stimuli and Signaling Cascades Implicated in Mediating Pathological and Physiological Cardiac Hypertrophy

In settings of increased load under disease conditions or in response to exercise, cardiac myocytes are subjected to mechanical stretch and numerous stimuli and factors, including increased activation of the sympathetic nervous system, and autocrine and paracrine humoral factors such as angiotensin II (Ang II), endothelin 1 (ET-1), insulin-like growth factor 1 (IGF1), norepinephrine (NE), thyroid hormone transforming growth factor-β and neuregulin 1 (NRG1). These factors bind to receptors on cardiac cells which then activate intracellular signaling pathways that regulate processes associated with cardiac growth. In the last two decades it has become apparent that different factors and signaling cascades contribute to the induction of pathological and physiological cardiac growth (Fig. 12.2).

A number of reviews have extensively described the signaling pathways and molecular mechanisms responsible for mediating pathological cardiac hypertrophy

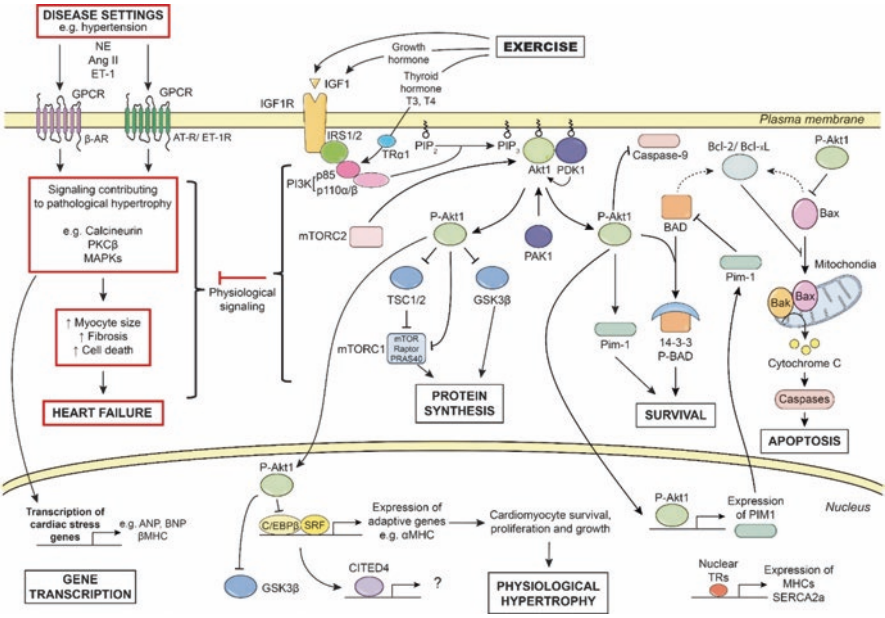

Fig. 12.2 A simplified schematic of components of the IGF1-PI3K-Akt signaling pathway, and the regulation of physiological cardiac hypertrophy and exercise-induced protection (e.g. via inhibition of apoptosis). The potential interaction of the IGF1-PI3K-Akt pathway inhibiting signaling cascades involved in mediating pathological cardiac hypertrophy and heart failure is also depicted. N.B. Not all interactions have been comprehensively defined in the adult heart and may involve multiple steps. Further studies will be required

[14, 25–28]. Some of these include G proteins (heterotrimeric and the small GTP binding proteins), protein kinase C (PKC), mitogen activated protein kinases (MAPKs), and calcineurin (Fig. 12.2). This chapter largely focuses on observations from genetic mouse models that have identified the IGF1-PI3K-Akt signaling pathway as a critical mediator of exercise-induced physiological cardiac hypertrophy.

4 Key Molecular Mechanisms Responsible for Exercise-Induced Cardiac Growth and Protection

The IGF1-PI3K-Akt signaling pathway is considered the primary signaling pathway responsible for mediating physiological cardiac hypertrophy induced by long-term exercise training. Activation of this signaling cascade has also been shown to protect the heart in mouse models of cardiac injury and cardiovascular disease, while reduced IGF1-PI3K-Akt signaling is detrimental for cardiac function and accelerates disease progression. Other proteins that have been implicated in exercise-induced cardiac protection include nitric oxide (NO) signaling, heat shock

proteins, neuregulin, and the transcription factors C/EBPβ and CITED4. This chapter is focused largely on the role of IGF1, PI3K and Akt. NO signaling is described in chapter 31 and C/EBPβ-Cited4 signaling is described in chapter 32.

4.1 IGF1-PI3K-Akt Signaling

Much of the evidence demonstrating a critical role for IGF1-PI3K-Akt signaling in exercise-induced hypertrophy and cardiac protection comes from gain- and loss-of-function genetically modified mouse models (see Fig. 12.3 and subsequent

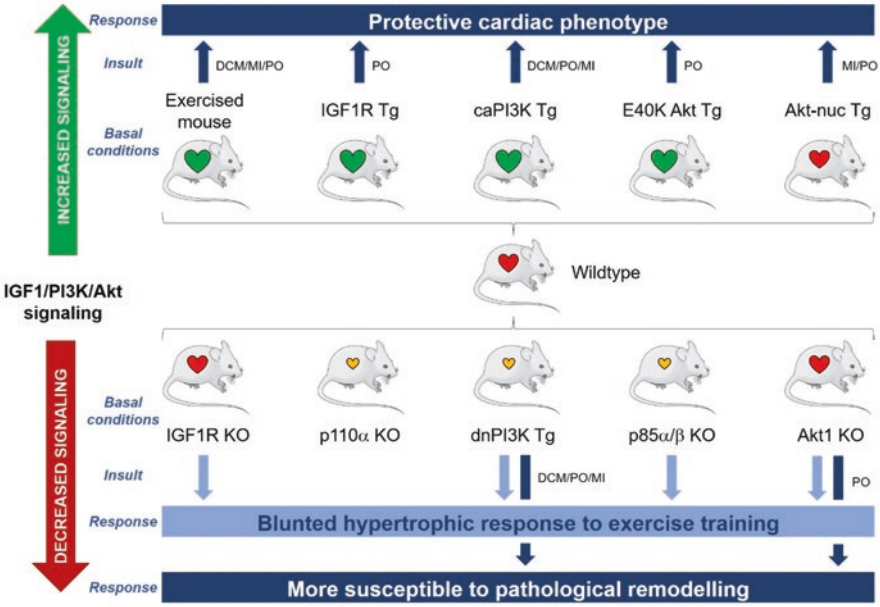

Fig. 12.3 Activation of the IGF1-PI3K-Akt pathway is required for physiological cardiac hypertrophy induced by exercise training and is cardioprotective. Genetically modified mice with elevated IGF1/PI3K/Akt signaling have normal heart size or develop physiological cardiac hypertrophy (denoted by larger heart symbols), whereas mice with reduced IGF1/PI3K/Akt signaling have normal or reduced heart size and display a blunted hypertrophic response to exercise training. Mice with elevated IGF1/PI3K/Akt signaling display cardiac protection in settings of dilated cardiomyopathy (DCM), myocardial infarction (MI) and pressure overload (PO), whereas mice with reduced IGF1/PI3K/Akt signaling are more susceptible to pathological remodeling. IGF1R Tg: cardiomyocyte-specific expression of human IGF1R [33]. caPI3K Tg: cardiomyocyte-specific expression of a constitutively active PI3K(p110α) mutant [49]. E40K Akt Tg: cardiomyocyte-specific expression of a constitutively active Akt mutant [74]. Akt-nuc: cardiomyocyte-specific expression of nuclear-targeted Akt [75]. IGF1R KO: cardiomyocyte-specific deletion of the IGF1R [32]. p110α KO: inducible cardiomyocyte-specific deletion of PI3K(p110α) [48]. dnPI3K Tg: cardiomyocyte-specific expression of a dominant negative PI3K(p110α) mutant [13, 49]. p85α/β KO: muscle-specific deletion of PI3K(p85α) in mice globally deficient for PI3K(p85β) [47]. Akt1 KO: global deletion of Akt1 [71]

sections). However, there is also evidence from human studies linking IGF1-PI3K signaling with physiological cardiac hypertrophy and cardiac protection. Cardiac formation of IGF1, but not Ang II or ET-1 (linked with pathological cardiac hypertrophy, Fig. 12.2), was elevated in athletes compared with healthy controls, and was positively correlated with left ventricle (LV) mass index [29].

4.1.1 IGF1R

IGF1 is a hormone that is released by the liver in response to growth hormone (GH) but can also be produced by the heart. IGF1 levels in the coronary sinus of resting athletes with LV hypertrophy was elevated compared with sedentary controls [29], and serum IGF1 levels increase in response to acute bouts of aerobic exercise (e.g. cycling [30]) and resistance training (e.g. repeated arm resistance exercise requiring concentric or eccentric skeletal muscle contractions [31]). Binding of IGF1 to the IGF1 receptor (IGF1R) leads to autophosphorylation of tyrosine residues within the intracellular domain and the recruitment of SH2 domain-containing proteins, such as the p85 regulatory subunit of class IA PI3K. Studies in genetically modified mice have demonstrated that IGF1R is an important regulator of physiological cardiac hypertrophy [32, 33]. Cardiomyocyte-specific overexpression of the IGF1R in mice led to a ~ 35% increase in heart weight, which was associated with enhanced systolic function at 3 and 12–16 months of age, indicative of physiological hypertrophy [33]. The IGF1R was shown to be critical for mediating physiological cardiac hypertrophy in response to exercise, as cardiac-specific IGF1R knockout mice did not develop LV hypertrophy when subjected to 36 days of swim training, a protocol that induces a robust hypertrophic response in wildtype mice [32].

4.1.2 PI3K

The p110α isoform of PI3K has been shown to be a critical regulator of: (i) postnatal heart growth, (ii) exercise-induced cardiac hypertrophy, and (iii) exercise-induced cardiac protection (details described below).

PI3Ks are lipid kinases that are involved in a wide range of cellular processes, including metabolism, cell cycle progression, cell survival, protein synthesis, cell polarity and motility and vesicle trafficking [34]. Of the three classes, class I PI3Ks have received the most attention with regards to cardiac hypertrophy. Class I PI3Ks consist of a catalytic subunit (p110α/β/δ for class IA; p110γ for class IB) and a regulatory subunit (p85/p55/p50 for class IA; p101/p87 for class IB) [35]. p110α and p85α are the predominant class IA catalytic and regulatory subunits expressed in heart, respectively [36, 37]. Exercise training increases cardiac PI3K(p110α) activity in mice [38], consistent with the increase in circulating IGF1 levels observed in mice and humans [29, 39–41]. PI3K(p110α) catalyses the phosphorylation of lipids in the plasma membrane to produce second messengers, such as phosphatidylinositol 3,4,5-trisphosphate (PIP_3) [42]. PIP_3 recruits enzymes, such as Akt in complex

with phosphoinositide-dependent protein kinase-1 (PDK1), from the cytosol to the plasma membrane for subsequent activation [43–46].

In cardiomyocytes, the subcellular localization and activity of PI3K(p110α) is regulated by the regulatory subunit p85 [37]. Deletion of either p110α or p85α/β, or cardiomyocyte-specific expression of a dominant negative (dn) PI3K(p110α) mutant, reduces heart size in mice (see Fig. 12.3), demonstrating an important role in postnatal cardiac development [47–49]. dnPI3K mice were also mated with IGF1R transgenic mice to investigate whether PI3K(p110α) is important for IGF1R-induced heart growth [33]. IGF1R-dnPI3K double transgenic mice displayed the same cardiac phenotype as dnPI3K mice, i.e. a reduction in heart size compared with control non-transgenic (Ntg) littermates, demonstrating that PI3K(p110α) is critical for mediating IGF1-induced physiological cardiac hypertrophy [33].

In contrast to dnPI3K mice, cardiomyocyte-specific expression of a constitutively active (ca) PI3K(p110α) (caPI3K) mutant induces physiological cardiac hypertrophy, characterized by a ~ 20% increase in heart mass, preserved cardiac function, and the absence of histopathology [13, 49]. Yano and colleagues developed an inducible transgenic mouse expressing the same caPI3K construct present in the caPI3K transgenic mice described above [50]. Cardiac hypertrophy was observed after 2 months of transgene expression [50]. Shorter periods of transgene expression increased expression of Ca^{2+}-handling proteins (e.g. SERCA2a) and enhanced cardiomyocyte contractility in the absence of hypertrophy, demonstrating that PI3K(p110α) positively regulates cardiomyocyte contractility independently of its effects on cardiomyocyte size [50].

After demonstrating that PI3K(p110α) was critical for physiological postnatal heart growth [49], the role of PI3K(p110α) in mediating physiological exercise-induced hypertrophy was examined [13]. PI3K(p110α) activity was elevated in hearts of mice after 2 weeks of swim training or treadmill running [51]. PI3K(p110α) was identified as a critical regulator of exercise-induced cardiac hypertrophy, as dnPI3K mice displayed a blunted hypertrophic response to exercise training, despite having the same exercise capacity as non-transgenic littermates [13]. A similar phenotype was observed in mice deficient for p85α/β [47] (see Fig. 12.3).

Finally, PI3K(p110α) was also shown to be an important regulator of exercise-induced cardiac protection in a cardiac disease model (pressure overload induced by ascending aortic banding). Swim training prior to aortic banding blunted pathological cardiac hypertrophy and prevented the development of cardiac fibrosis and cardiac dysfunction in Ntg mice [52]. Banded dnPI3K mice displayed faster disease progression than untrained Ntg mice. Swim training had no protective effect in dnPI3K mice, based on fractional shortening, heart size, atria size, fibrosis and gene expression. In contrast, caPI3K mice were protected from pathological remodeling and the development of cardiac dysfunction, regardless of whether or not mice were exercised prior to the induction of pressure overload [52]. These data strongly suggest that PI3K(p110α) is an important mediator of exercise-induced cardiac protection. One limitation of this study is that PI3K(p110α) activity was reduced in dnPI3K mice throughout the entire experimental protocol, as opposed to only during the exercise training period. However, if exercise was providing any significant protection independently of PI3K(p110α), one would expect to observe some degree

of protection in trained dnPI3K mice compared with untrained controls. Thus, collectively the data support the hypothesis that PI3K(p110α) is an important mediator of exercise-induced cardiac protection [52].

It is also noteworthy that other genes associated with exercise-induced cardiac protection such as heat shock proteins and *Cited4* are also upregulated in hearts of caPI3K mice [52–61]. Thus, these alterations in gene expression may represent some of the mechanisms by which PI3K(p110α) protects the heart during exercise. Given that PI3K(p110α) lies upstream of numerous signaling pathways and regulates a large number of genes (not limited to those listed above [62]), it is possible that PI3K(p110α) protects the heart via activation of multiple, parallel signaling pathways.

4.1.3 Akt

Akt (also known as protein kinase B), is a well characterized target of PI3K. As described earlier, PIP_3 acts as a docking site for Akt and PDK1 (Fig. 12.2). Akt is activated by phosphorylation at Ser473 by mTOR complex 2 (mTORC2; [63]), and subsequent phosphorylation at Thr308 by PDK1 [63, 64]. Phosphorylation at both residues is critical for maximal kinase activity [65]. Following activation, Akt can phosphorylate cytosolic, nuclear or mitochondrial targets, such as GSK3β [66] and tuberous sclerosis complex 2 (TSC2) [67]; both contributing to the regulation of heart size. Phosphorylation of TSC2 leads to activation of mTOR complex 1 (mTORC1; contains regulatory associated protein of mTOR, Raptor; [68, 69]) (Fig. 12.2).

Of the three Akt isoforms (Akt1, Akt2, Akt3), Akt1 and Akt2 are the most abundant in the heart [70]. Studies suggest that Akt1 is the main isoform involved in regulating exercise-induced physiological cardiac hypertrophy and is the focus of this section [71]. Numerous Akt transgenic mouse models with increased Akt activity have been generated with a spectrum of phenotypes reported. These have ranged from the absence of hypertrophy associated with cardiac protection to significant hypertrophy associated with a pathological phenotype and premature death [72–75]. The different cardiac phenotypes observed in Akt transgenic mouse models may be due to differences in the level and duration of transgene expression, the subcellular localization of the translated transgene, and whether the rate of coronary angiogenesis is able to maintain vascular density of the hypertrophied myocardium [76]. Some key examples are provided below.

Shioi and colleagues generated cardiac-specific constitutively active (ca) and kinase-deficient (kd) Akt transgenic mice to investigate the role of Akt in regulating heart size [72]. Cardiac Akt activity was increased 80-fold in caAkt mice and reduced by approximately 45% in kdAkt mice. caAkt mice displayed cardiomyocyte hypertrophy, extensive interstitial fibrosis and depressed systolic function at 14 weeks of age, indicative of pathological cardiac hypertrophy. In contrast, reduced Akt activity had no effect on heart weight under basal conditions. Reducing Akt activity in hearts of caPI3K mice (by crossing caPI3K mice with kdAkt mice) significantly blunted the degree of cardiac hypertrophy in caPI3K mice, and reducing PI3K(p110α) activity in hearts of caAkt mice (by crossing dnPI3K mice with caAkt

mice) did not affect the degree of hypertrophy in caAkt mice [72]. Thus, even though caAkt mice developed pathological cardiac hypertrophy, rather than physiological cardiac hypertrophy, this study provides evidence that Akt acts downstream of PI3K to induce hypertrophy. Cardiac-specific transgenic mice expressing a different constitutively active Akt mutant (E40K AKT mice) displayed cardiac hypertrophy with preserved systolic function [74] (Fig. 12.3). E40K Akt transgenic mice displayed evidence of enhanced cardiomyocyte contractility, and this was associated with increased SERCA2a expression [77]. Finally, cardiac-specific transgenic mice overexpressing an Akt mutant which localized to the nucleus (nuclear-targeted Akt) had normal heart size and function under basal conditions, and displayed a protective phenotype in settings of myocardial infarction and pressure overload [75, 78] (Fig. 12.3). The generation of a cardiac-specific inducible transgenic mouse, expressing myristoylated (myr) Akt1 in the absence of doxycycline, appears to explain, at least in part, why different Akt transgenic mouse models display different cardiac phenotypes [79]. myrAkt1 expression for 2 weeks led to physiological cardiac hypertrophy with preserved contractile function, which was completely reversible upon re-administration of doxycycline [79]. In contrast, 6 weeks of myrAkt1 expression led to pathological cardiac hypertrophy, which was associated with cardiac fibrosis, reactivation of the fetal gene program, depressed systolic function and reduced capillary density [79]. Systolic function continued to decline upon re-administration of doxycycline, demonstrating that the damage was irreversible [79]. Thus, while short-term activation of Akt1 leads to physiological cardiac hypertrophy, long-term activation is detrimental and leads to pathology.

The pathological phenotype of mice expressing myrAkt1 for 6 weeks was attributed to inadequate angiogenesis as the heart continued to hypertrophy. Vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2) are growth factors that jointly induce angiogenesis [80]. Expression of VEGF-A and Ang-2 was significantly increased in hearts of mice with physiological cardiac hypertrophy induced by 2 weeks of myrAkt1 expression, suggesting that Akt plays a dual role during cardiac hypertrophy, promoting angiogenesis as well as cell growth [79]. Adenoviral expression of the VEGF scavenger, Flk-Fc, blocked physiological cardiac hypertrophy induced by 2 weeks of myrAkt1 expression [79]. Instead of developing physiological cardiac hypertrophy, mice displayed LV dilation and systolic dysfunction, demonstrating that disruption of angiogenesis during the development of cardiac hypertrophy leads to contractile dysfunction [79].

Despite the different phenotypes of transgenic mice with increased Akt activation, Akt1 is considered a key regulator of exercise-induced cardiac hypertrophy. Akt1-deficient mice (*Akt1*$^{-/-}$ mice) were indistinguishable from wildtype littermates under basal conditions, demonstrating that Akt1 is not essential for postnatal heart growth [71]. However, loss of Akt1 prevented the development of cardiac hypertrophy in response to exercise training but not to pressure overload (Fig. 12.3), suggesting that Akt1 is critical for exercise-induced heart growth [71]. These findings are consistent with those in mice with reduced PI3K activity [13, 47].

More recently, other components/regulators of the IGF1-PI3K-Akt pathway, such as insulin receptor substrate (IRS) adaptor proteins (IRS1/IRS2) IRS1/2 [81], PDK1 [82], P21-activated kinase (PAK1; a potential PDK2) [83], and Proline Rich Akt Substrate of 40KDa (PRAS40; a binding protein that inhibits the mammalian target of rapamycin complex 1 [mTORC1]) [84] have also been shown to regulate exercise-induced cardiac hypertrophy (Fig. 12.2**).**

4.2 Other Factors Contributing to Exercise-Induced Cardiac Hypertrophy and Protection

While the focus of this chapter is the IGF1-PI3K-Akt signaling pathway, it is noteworthy that other growth factors can activate PI3K and/or Akt signaling (e.g. neuregulin), and other downstream effectors (e.g. C/EBPβ-CITED4) and signaling pathways can contribute to aspects of exercise-induced hypertrophy and protection. The role of NO signaling and C/EBPβ-CITED4 signaling is described in chapters 31 and 32, respectively. Thyroid hormone can also be regulated in response to exercise and may play a role by interacting with PI3K signaling (described below, Fig. 12.2). Two biologically active hormones, thyroxine (T_4, prohormone) and triiodothyronine (T_3), are secreted from the thyroid gland. Both diffuse across the plasma membrane and T_4 is converted to T_3 [85, 86]. Animal studies suggest that thyroid hormone is a critical regulator of normal postnatal heart growth. Heart growth was reduced in a setting of low thyroid gland activity, but increased with administration of excess thyroid hormone [87, 88]. In patients with chronic hyperthyroidism or humans administered T_4, heart mass is often increased and this is associated with normal or increased cardiac contractility [89–91]. Thus, cardiac enlargement in response to thyroid hormone has generally been classified as physiological.

The actions of thyroid hormone in the heart are most likely due to nuclear transcriptional mechanisms as well as membrane-initiated effects (Fig. 12.2). T_3 enters the nucleus and binds to nuclear thyroid hormone receptors (TRs), which act as transcription factors to directly activate or repress cardiac-related genes such as α- and β-MHC, and SERCA2a [85, 86, 92–98]. Of the two genes encoding TRs in mammals, TRβ appears to be more predominant than TRα in regulating cardiac growth [99].

Cytosolic and membrane-initiated effects of thyroid hormones have been reported [100, 101]. Cytosol-localized TRα1 can directly interact with the p85α regulatory subunit of PI3K in neonatal rat ventricular myocytes [102]. This interaction was shown to be necessary for T_3-induced protein synthesis. Thus, the T_3 mediated activation of PI3K by TRα1 may explain how thyroid hormone could induce physiological heart growth [102] (Fig. 12.2).

4.3 IGF1-PI3K(p110α)-Akt Signaling Is Cardioprotective in Preclinical Models

There is substantial evidence to demonstrate that enhanced IGF1-PI3K-Akt signaling can provide benefit in preclinical rodent cardiac disease models including pressure overload, MI, dilated cardiomyopathy (DCM), atrial fibrillation and diabetic cardiomyopathy [33, 62, 103–105]. Some of these studies are summarized in the subsequent text and Fig. 12.3.

4.3.1 IGF1 and PI3K(p110α) Attenuate Pathological Remodeling Induced by Pressure Overload

In wildtype / Ntg mice, pressure overload induced by aortic banding leads to pathological cardiac hypertrophy, increased interstitial fibrosis, reactivation of the fetal gene program and downregulation of SERCA2a mRNA expression [13, 103, 106, 107]. Transgenic overexpression of the IGF1R or expression of caPI3K(p110α) blunted cardiac hypertrophy and reduced the degree of interstitial fibrosis in these models [33, 103]. caPI3K transgenic mice also had enhanced systolic function compared with Ntg mice [103], demonstrating that increasing PI3K(p110α) activity is protective.

4.3.2 PI3K(p110α) Improves Survival in a Setting of DCM

The low levels of Cre recombinase used to delete floxed genes in conditional knockout mouse models are not cardiotoxic [108]. However, transgenic mice expressing high levels of Cre recombinase (DCM-TG9 mice) develop a severe DCM phenotype and die prematurely [108]. Twice-daily exercise training from 4 weeks of age improved lifespan of DCM-TG9 mice by approximately 20% [103]. It was suggested that exercise-induced activation of PI3K(p110α) may be responsible for the cardioprotection observed in these mice, as PI3K(p110α) is activated in the heart by exercise [51] and is critical for the induction of physiological cardiac hypertrophy in response to exercise [13, 47]. Furthermore, increasing PI3K(p110α) activity in the hearts of DCM mice (by crossing DCM mice with caPI3K transgenic mice) had the same effect as swim training (~20% increase in lifespan; [103]).

4.3.3 PI3K(p110α) Improves Systolic Function in Mice with MI

Permanent ligation of the left coronary artery induces MI in mice. caPI3K transgenic mice had improved systolic function compared with Ntg mice 8 weeks post-MI [62]. These data demonstrate that increasing PI3K(p110α) activity can also provide protection in a setting of ischemic heart disease.

4.3.4 Reducing Cardiac PI3K(p110α) Activity Accelerates Disease Progression

In each of the models described above (pressure overload induced by aortic banding, DCM and MI), increasing cardiac PI3K(p110α) activity provided a degree of protection against pathological remodeling and the development of heart failure. Reducing cardiac PI3K(p110α) activity in each of these models accelerated disease progression, demonstrating that PI3K(p110α) is important for protecting the heart in settings of CVD. For example, expression of the dnPI3K mutant in DCM-TG9 mice reduced lifespan from ~85 days to ~40 days [103]. dnPI3K mice displayed a greater degree of pathological cardiac hypertrophy, increased fibrosis, reduced SERCA2a mRNA expression and poorer systolic function compared with Ntg mice in response to pressure overload induced by aortic banding [13, 103], and a greater degree of cardiac dysfunction after 8 weeks of MI [62]. *Akt1*$^{-/-}$ mice displayed a similar phenotype to dnPI3K mice when subjected to aortic banding (i.e. a greater degree of cardiac hypertrophy and worse systolic function than control mice) [71].

In summary, increasing PI3K(p110α) signaling attenuates pathological remodeling in mouse models of CVD, whereas decreasing cardiac PI3K(p110α) activity exacerbates pathological remodeling and accelerates disease progression.

4.3.5 Akt Protects the Heart by Promoting Cell Survival and Angiogenesis

Akt protects the heart, largely, by promoting cardiomyocyte survival and coronary angiogenesis [75, 79, 109–114]. E40K AKT transgenic mice displayed less pathological remodeling and had better heart function than wildtype controls following aortic banding, which was associated with increased VEGF expression, increased capillary density, reduced apoptosis and reduced fibrosis [113] (Fig. 12.3).

Akt suppresses apoptosis via multiple mechanisms. Akt phosphorylation of caspase-9 inhibits protease activity, while phosphorylation of inactive procaspase-9 prevents cleavage and subsequent caspase-9 activation [115]. Akt also promotes cell survival via the phosphorylation of pro-apoptotic Bcl-2 family members. Phosphorylation of BAD promotes association with 14-3-3 proteins, alleviating the inhibitory effects of BAD on pro-survival proteins Bcl-2 and Bcl-x_L [116–118], while phosphorylation of Bax prevents mitochondrial translocation and subsequent cytochrome *c* release [119].

Proviral integration site for Moloney murine leukemia virus-1 (Pim-1) is a serine/threonine kinase that mediates cell survival downstream of Akt [120]. Nuclear Akt increases Pim-1 expression, leading to enhanced phosphorylation of BAD and increased expression of Bcl-2 and Bcl-x_L [120, 121]. Loss of Pim-1 increased apoptosis and accelerated pathological cardiac remodeling in mice subjected to MI or

aortic banding, and cardiac-specific overexpression of Pim-1 reduced infarct size in mice subjected to MI [120].

5 Therapeutic Strategies Targeting the IGF1-PI3K-Akt Pathway

Heart failure research and therapy has generally focused on identifying and inhibiting processes associated with pathological hypertrophy, cardiac dysfunction, and the transition to heart failure. Targeting signaling pathways that play distinct roles in regulating physiological hypertrophy may represent another approach. As described earlier, enhanced IGF1-PI3K-Akt signaling in the heart has beneficial effects in numerous models of cardiac stress, hypertrophy and failure [33, 62, 103, 122–126]. Increased activation of the IGF1-PI3K-Akt pathway was associated with better outcomes in terms of cardiac function, lifespan or cardiac fibrosis. In contrast, a reduction of PI3K or Akt had adverse effects on cardiac function, fibrosis and/or lifespan in heart failure mouse models [13, 52, 62, 71, 103–105]. The IGF1-PI3K-Akt pathway appears to confer cardiac protection via a number of mechanisms including cell survival (anti-apoptotic), angiogenesis, maintenance of SERCA2a gene expression, and induction of anti-fibrotic properties. An additional advantage of activating physiological signaling pathways may be related to an ability of PI3K and/or Akt to inhibit components of pathological signaling cascades [71, 103, 127].

While there is compelling evidence to demonstrate that activating the IGF1-PI3K-Akt pathway in the heart has beneficial effects, there are on-going questions and challenges in directly targeting this pathway. For example, while studies in rodent and large animal models of MI identified IGF1 administration as a potential therapeutic strategy for the treatment of heart failure [128–133], results from clinical trials with chronic administration of IGF1 to humans were not favorable [134, 135]. A potential explanation for the disappointing results may be a consequence of chronic IGF1 acting on cardiac fibroblasts and promoting fibrosis. This highlights the numerous actions of the IGF1-PI3K-Akt pathway in different cardiac cell types, but also other organs. For instance, PI3K(p110α) permits cancer cells to bypass normal growth-limiting controls [136]. Consequently, if this pathway is to be targeted it will be important to identify strategies for targeting cardiac cells of interest selectively or specifically.

5.1 Gene Therapy Approaches

Gene therapy approaches that selectively target the heart using adeno-associated viral vectors and/or novel delivery tools represent an active area of research [137]. We developed a gene therapy (recombinant adeno-associated virus, rAAV) to deliver caPI3K (p110α; same construct as the caPI3K mice) to hearts of adult mice

with established cardiac pathology [52]. The combination of recombinant AAV serotype 6 (rAAV6) with the CMV promoter allows for selective expression in cardiac myocytes [52, 138]. Administration of rAAV6-CMV-caPI3K for 8 weeks led to physiological cardiac hypertrophy in normal adult mice, and this mimicked the hypertrophy previously observed in caPI3K mice [52]. In a cardiac disease model of pressure overload with established hypertrophy and dysfunction, rAAV6-CMV-caPI3K improved heart function [52]. PI3K(p110β) has also been targeted with another cardiac-selective AAV serotype (rAAV9). Delivery of rAAV9-PI3K(p110β) in mice after MI was shown to improve cardiac myocyte survival via mechanisms involving proliferation and reduced apoptosis [139]. Akt gene therapy approaches have also shown promise in models of ischemia-reperfusion and heart failure [110, 112, 140]. To our knowledge, a cardiac selective AAV approach with Akt has not been reported *in vivo*. However, delivery of human *PIM-1* (downstream of Akt, Fig. 12.2) to the heart using a rAAV9 blunted cardiomyocyte apoptosis and improved diastolic function in mice with diabetic cardiomyopathy [141].

5.2 Small Molecules Activating the IGF1-PI3K-Akt Pathway

While small molecules administered orally will not target cardiac myocytes specifically, agents with short half-lives may have the potential to mimic the intermittent nature of exercise. A small molecule (BGP-15) which was shown to phosphorylate the IGF1R provided benefit in two mouse models which develop heart failure and are susceptible to atrial fibrillation [142]. By contrast, a small molecule which activates Akt (SC79) provided no significant benefit in a model of ischemia-reperfusion [143]. The negative results with SC79 may be related to timing or dose.

5.3 PI3K Regulated-microRNAs

Studies conducted over the last two decades have demonstrated an important role for microRNAs (miRNAs, small non-coding RNA molecules), in a range of biological and disease processes [144–147]. MiRNAs can regulate the expression of hundreds of target genes, typically by binding to complementary "seed" sequences in the 3′ untranslated region of target mRNAs, which results in gene silencing and inhibition of protein synthesis [148]. The global role of miRNA function in the heart was demonstrated by deleting Dicer (critical for miRNA maturation) in the murine heart [149, 150]. This resulted in mutant mice with depressed heart function and severe heart failure, revealing the importance of miRNAs in cardiomyocyte homeostasis. Furthermore, miRNA expression profiling studies demonstrate altered expression levels of specific miRNAs in diseased human hearts (compared to normal control hearts), implicating a role for miRNAs in cardiomyopathies [151, 152]. A number of preclinical studies have identified miRNAs that play key roles in

regulating processes associated with pathological cardiac hypertrophy [153–157]. Recently, investigators have identified miRNAs associated with exercise, physiological cardiac hypertrophy and PI3K signaling (reviewed in [158]). The beneficial effects of miRNAs and other non-coding RNAs in mediating the beneficial effects of exercise are described in Chapter 33. Using cardiac-specific transgenic mice with increased or decreased PI3K(p110α) activity, we identified miRNAs that were differentially regulated in a setting of physiological hypertrophy and cardiac protection (due to activation of PI3K(p110α)) versus a model of cardiac stress associated with pathological growth [62]. We subsequently showed that targeting PI3K-regulated miRNAs (miR-34, miR-34a, miR-652 or miR-154) was associated with better heart function in cardiac disease mouse models (e.g. MI, aortic-banding or DCM) [159–163].

6 Summary

A challenge for the cardiac biology field is to identify and translate strategies with the ability to improve function of the failing heart. Given exercise is an intervention which can improve heart function and reverse LV remodeling in heart failure patients [164], targeting key regulators of exercise-induced hypertrophy and protection could represent a promising approach. The generation and characterization of genetic mouse models in response to pathological and physiological stimuli have allowed investigators to identify signaling pathways and proteins responsible for mediating distinct forms of cardiac growth. The IGF1-PI3K-Akt pathway is a critical signaling pathway for the induction of exercise-induced hypertrophy and protection. Activation of IGF1-PI3K-Akt signaling alone, or in combination with inhibition of signaling pathways responsible for mediating pathological hypertrophy, may have benefits above inhibiting pathological processes alone. However, novel approaches for selectively targeting the IGF1-PI3K-Akt pathway in the heart may be required to avoid adverse consequences in other cell types.

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Chapter 13
NO Signaling in the Cardiovascular System and Exercise

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Abstract Nitric oxide (NO) is a small molecule implicated in multiple signal transduction pathways thus contributing to the regulation of many cellular functions. The identification of NO synthase (NOS) isoforms and the subsequent characterization of the mechanisms of cell activation of the enzymes permitted the partial understanding of both the physiological and pathological processes. NO bioavailability plays an important role in the pathophysiology of cardiovascular disease and its reduction in endothelial cells is strictly associated to endothelial dysfunction which, in turn, correlates with cardiovascular mortality. Indeed, endothelial NO synthase (eNOS) has a key role in limiting cardiac dysfunction and remodeling in heart diseases, in part by decreasing myocyte hypertrophy. Conversely, exercise training is recommended to prevent and treat cardiovascular diseases-associated disorders at least by enhanced NO synthase activity and expression, and increased production of antioxidants, which prevents premature breakdown of NO. Exercise training may cause an improvement in endothelial function for both experimental animals and humans; Studies in both healthy subjects and patients with impaired NO-related vasorelaxation remarked exercise training ability to improve vascular structure and function and endothelial homeostasis. This chapter will briefly consider the importance of NO signaling in the maintenance of cardiovascular physiology, and discuss recent insights into the effect of exercise

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training on the signaling pathways that modulate NO synthesis and degradation in health and cardiovascular disease. In addition, we will highlight the molecular mechanisms via which microRNAs (miRs) target NO signaling in the cardiovascular system, and NO as a candidate molecule for development of new therapies.

Keywords Cardiomyocytes • Exercise • NO • microRNAs

1 Introduction

Nitric oxide (NO) is a widespread biological mediator implicated in many physiological and pathological processes [1–4]. In 1980, the endothelium-dependent relaxation and the existence of the endothelium-derived relaxing factor (EDRF) were described by Furchgott and Zawadzki [5] demonstrating that the endothelium had the capacity to release a vasoactive substance in response to acetylcholine. In 1987, EDRF was identified by Ignarro et al. [6] as an inorganic gas called NO, a compound which caused smooth muscle cell relaxation. For their norm-breaking discoveries regarding the effects of NO on the cardiovascular system, Robert F. Furchgott, Ferid Murad and Louis J. Ignarro were awarded the Nobel Prize of Physiology or Medicine in 1998. As a consequence of its importance in neuroscience, physiology, and immunology, NO was proclaimed "Molecule of the Year" in 1992 [7]. Now, 30 years later, NO research has progressed considerably and gained status as one of the most important signaling molecules and yielded many unexpected insights into cardiovascular control [1, 2, 8–10].

NO has been the most studied endothelium-derived relaxing factor among the substances which cause relaxation of vascular smooth muscle. Its intrinsic vasodilator function is commonly used as a surrogate index of endothelial function and essential to preserve cardiovascular physiology [2–4, 9, 11]. Although known for its multiple roles in vasodilatation, vascular remodeling, neurotransmission, inhibition of platelet aggregation and leukocyte-endothelium adhesion, cardiac contractility and immune defense; NO also acts as an intracellular messenger for several cells in the organism [1–4, 8–10].

NO plays an important role in the protection against the onset and progression of cardiovascular disease. Reduced bioavailability of NO is thought to be one of the central factors to endothelial dysfunction which, in turn, correlates with cardiovascular mortality [1–4, 8, 9]. In contrast, studies have documented the protective effects of exercise training on cardiovascular diseases [11–15]. The mechanisms involved in mediating these benefits are associated to enhance NO synthase activity and expression, and to increase the production of antioxidant, which prevents premature breakdown of NO (Fig. 13.1) [1, 11–15]. Therefore, NO can be to consider a promising therapeutic candidate for cardiovascular disease. In this way, genetic and molecular approaches have contributed significantly to our understanding of

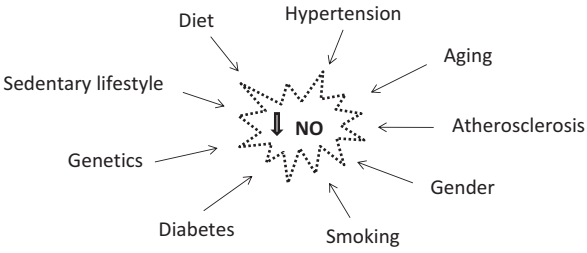

Fig. 13.1 Reduced bioavailability of NO associated with cardiovascular diseases and lifestyle factors

responses mediated by NO signaling in both physiological and pathological conditions [1–4, 8, 10, 15].

This chapter will briefly consider the importance of the NO signaling in the maintenance of cardiovascular physiology, and discuss recent insights over the effect of exercise training into the signaling pathways that modulate NO synthesis and degradation in healthy and cardiovascular disease. In addition, we will highlight the molecular mechanisms via microRNAs (miRs) targeting NO signaling in the cardiovascular system and NO as a candidate molecule for development of new therapies.

2 Nitric Oxide Synthases

NO can be generated by three different isoforms of the enzyme NO synthase (NOS): neuronal NOS (nNOS, NOS-1), inducible NOS (iNOS, NOS-2), and endothelial NOS (eNOS, NOS-3). All isoforms are expressed in the cardiovascular system. They utilize L-arginine and molecular oxygen as substrates and require the cofactors reduced nicotinamide-adenine-dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), and (6R-)5,6,7,8-tetrahydrobiopterin (BH4). The gene encoding eNOS is located on chromosome 7, the gene for nNOS is on chromosome 12 and that for iNOS is on chromosome 17. The three isoforms are conserved between the species; share homologies in regions involved cofactor binding and have similar enzymatic mechanisms that involve electron transfer for oxidation of L-arginine. However, expression pattern and enzyme activity regulation differ between them [1, 2, 4, 9, 16]. Curiously, Ghafourifar et al. identified mitochondrial NOS (mtNOS). The author showed mtNOS is located in the inner mitochondrial membrane involved with mitochondrial bioenergetics and survival [17].

The NO generated may produce physiological effects but can also be toxic to cells. Generally, nNOs and eNOS are expressed constitutively in neurons and endothelial cells, respectively, though they can also be expressed by other cells. These isoforms are associated with the maintenance of the cardiovascular integrity and function. Activation of these two isoforms depends on calcium ions and calmodulin, resulting in NO production in the nanomolar concentration. Conversely, iNOS was initially

Table 13.1 Functions of the different NOS isoforms

NOS isoforms	Initially discovered	Function
eNOS	Endothelium	Vasodilation,
		Vascular remodeling,
		Inhibition of platelet aggregation and leukocyte-endothelium adhesion,
		Cardiac contractility.
nNOS	Neurons	Synaptic plasticity (learning and memory formation),
		Neurotransmitter
		Vasodilation,
		Penile erection.
iNOS	Macrophages	Immune defense,
		Mediation of inflammation,
		Septic shock.

discovered in macrophages and its expression typically requires inflammatory states by cytokines or bacterial products, but its role in the cardiovascular inflammatory process is still unclear (Table 13.1). Indeed, once expressed iNOs is fully active and generates large quantities of NO. iNOS isoform binds calmodulin tightly so that its activity is functionally independent of prevailing concentration of calcium. Most cells do not express iNOS constitutively, although constitutive expression of iNOS has been described in the rat kidney [1, 2, 4, 9, 16, 18].

NOS monomers are capable of transferring electrons from NADPH to FAD and FMN and bind calmodulin, which enhances electron transfer within the reductase domain, but it is unable to bind the cofactor BH4 or the substrate L-arginine and cannot catalyze NO production [4, 9, 16, 19, 20]. For functional NOS, NOS proteins must dimerize and the haem is essential for the interdomain electron transfer from the flavins to the haem of the opposite monomer. Therefore, increased levels of intracellular calcium activate calmodulin, which binds to eNOS and facilitates electron flow from the NADPH in the reductase domain of eNOS to the haem in the oxygenase domain (Fig. 13.2). Recently, Chen et al. [21] showed that eNOS dimerization is regulated by heat shock protein 90 (HSP90) rather than by phosphorylation, indicating eNOS dimerization is essential for enzymatic activity and NO production. In the absence of L-arginine or BH4, eNOS is uncoupled and the monomer form of eNOS synthesizes superoxide (O_2^-) in preference to NO [1, 2, 4, 9, 20, 22]. During conditions of inflammatory and oxidative stress, superoxide is generated from uncoupled eNOS and the activation of oxidase enzymes, such as NADPH oxidases (NOXs) and xanthine oxidase (XO), which can react with NO to form peroxynitrite ($ONOO^-$). This process show pathological mechanism underlying the progressive decrease in NO bioavailability in the cardiovascular diseases [1–4, 9, 16, 18, 23].

Curiously, the generation of NO is not restricted to NOS. Source of NO is the ingestion of dietary (inorganic) nitrate which decomposes to NO and other nitrogen

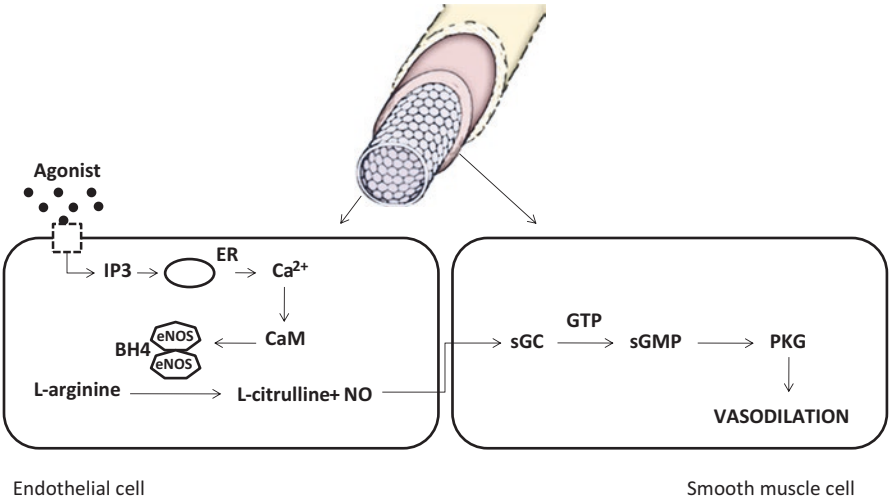

Fig. 13.2 NO signaling in the vascular system (NO synthase, in presence of cofactors (BH4), converts L-arginine to L-citrulline and NO in the endothelium in response to agonists and other stimuli, such as, shear stress. Binding of agonist to G protein receptors causes inositol trifosfato (IP3) production. IP3 releases calcium ions (Ca^{2+}) from endoplasmic reticulum (ER). Ca^{2+} and calmodulin (CaM) form complex which stimulates NO synthase to produce NO. NO diffuses from endothelial cell into adjacent smooth muscle cells. In smooth muscle cell, NO activates soluble guanylyl cyclase (sGC) to make cyclic GMP (cGMP). cGMP activates protein kinase G (PKG) which phosphorylates several muscle proteins to induce muscle relaxation

oxides via entero-salivary circulation. Studies showed that the consumption of nitrate-rich food such as fruits, leafy vegetables, and cured meals or nitrate supplementation along with antioxidants can compensate for any disturbance in endogenous NO, associated with decrease in blood pressure and reduction the risk of ischemic stroke [24, 25].

3 Intracellular Nitric Oxide Targets and Genetic Approaches

The biological responses of NO are regulated by its free radical nature and reactivity with other radicals and transition metals [1, 2, 4, 9]. Intracellular NO targets act in molecular recognition of NO and in the switching mechanism that transduces the chemical signal into a functional response [26]. NO readily diffuses from the cell membrane into the active extracellular space in the tissues, limited only by the half-life (1–2 milliseconds) and chemical reactivity. Subsequently, NO because it is a major nitrogen reactive species that induce quaternary reactions sulfhydryl group nitrosylation (formation of S nitrosylation or disulfide) or cysteine residues (for sulfinic and sulfinic acid) and its can interact with free radicals to induce a variety of biological responses [1, 2, 10, 26].

NO is a renowned modulator of vast processes in the nervous, immune, and cardiovascular systems. NO is a response intermediary through interaction with multiple signaling pathways. A target of NO is guanylate cyclase (sGC) that subsequently acts on target proteins. NO stimulates the sGC via S-nitrosylation of its ferrous (Fe^{2+}) heme center, which elevates basal catalytic conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) (Fig. 13.2). The basal activity of sGC is extremely low, but when NO binds to the haem moiety, the activity increases over 400 fold. An increase in the intracellular concentration of cGMP leads to a wide variety of secondary effects including vasodilation, nerve signaling, mitochondrial biogenesis and angiogenesis [1, 2, 9, 10, 18, 27]. Phosphodiesterases have been involved with its signaling pathway by hydrolyze cGMP. cGMP can both inhibit phosphodiesterase 3 and increase phosphodiesterase 5 enzyme activity, leading to promotion or counteraction of NO–sGC–cGMP signaling, respectively [1]. In addition, the high affinity of NO for transition metals also underlies its reversible inhibition of cytochrome c oxidase, acting as a mitochondrial permeability transition pore opening inhibitor which exerts a cell protecting effect [27].

The non-classical signaling pathway of NO involving cysteine S-nitrosation and S- glutathionylation, and tyrosine nitration are known as post-translational alterations of proteins, considered as potential mechanisms for cell cycle regulation in cardiovascular system [1, 27, 28]. There are a large number of proteins affected by these reactions and the effect can be either beneficial or harmful, which adds to the complexity of NO signaling pathways. The effect of NO on the cellular processes depends on its concentration and the presence of other free radicals. Low concentrations of NO (pM to nM) may promote cell proliferation, whereas high concentrations (μM) tend to affect cells indirectly by oxidative and nitrosative stresses leading to cell cycle arrest or apoptosis [2, 4, 9, 10, 29]. These are thought to be due to the generation of $ONOO^-$, a product of the reaction between NO and O_2^-. If produced at the mitochondrial level $ONOO^-$ can irreversibly inhibit complex I-III, causing cytotoxicity. It may also cause damage by nitrating tyrosine residues on proteins. However, $ONOO^-$ may be inactivated by combining with range molecules such as thiols, low molecular mass antioxidants and sugars. Therefore, $ONOO^-$ appears to be critically dependent on the local concentration of thiols and other molecules that may act as scavengers [1, 4, 18, 30].

Elucidation about impair or otherwise amplify NO effects comes from genetically engineered mice. This complements pharmacological approaches because their specificity is at the genetic level. It identifies the roles of the individual NOS genes, since many tissues contain the three major NOS isoforms. In addition, it allows the study of how the chronic absence of the NOS isoform affects the physiology [1, 10, 31]. eNOS knockout mice show systemic hypertension, consistent with the role of eNOS in reducing vascular tone [31], showing also impairment of angiogenesis and smooth muscle cell proliferation, all of which are important in cardiovascular homeostasis [32]. iNOs knockout mice are prone to infections, and their macrophages exhibit poor cytotoxicity against parasites and tumor cells [33]. nNOS knockout mice display hypertrophic pyloric stenosis, once its enzyme induce relaxing pyloric sphincter muscles. In addition, given the

role of NO production by nNOS in neurotransmission, aberrant behavior has been reported in male siblings [34].

4 Phosphorylation and Regulation of eNOS Activity

eNOS is mostly expressed in endothelial cells, but it has also been detected in cardiac myocytes, platelets, neurons, placenta and kidney tubular epithelial cells [9]. eNOS activity is regulated by intracellular calcium and phosphorylation levels. The vascular endothelium has receptors for a variety of substances including: insulin, leptin, statins, bradykinin, substance P, noradrenaline, adrenaline, serotonin, vascular endothelial growth factor (VEGF), insulin like growth factor 1 (IGF-1), and has ion channels capable of responding of changes in pressure, stretch or shear stress. As previously described, receptor occupation by an agonist, or the opening of certain ion channels, leads to elevation of intracellular calcium and this activates eNOS to generate NO. However, eNOS can also be activated by stimuli that do not produce sustained increases in intracellular calcium, but by phosphorylation level. This activation is mediated by phosphorylation of the enzyme on several serine (Ser), threonine (Thr) and tyrosine (Tyr) residues. Phosphorylation of Ser1177 stimulates the flux of electrons within the reductase domain and increases the calcium sensitivity of the enzyme [2, 9, 35]. The kinases that are responsible for Ser1177 phosphorylation include calcium/calmodulin-dependent protein kinase II (CAMKII), AMP-activated protein kinase (AMPK), protein kinase A (PKA), protein kinase B/AKT, checkpoint kinase 1 (Chk1) and PKG. Shear stress, VEGF, statins, 8-Br-cAMP and bradykinin also lead to phosphorylation or dephosphorylation of sites on eNOS such as Ser615 by AKT, Ser633 by PKA and Pim1, Tyr657 by protein tyrosine kinase 2 (PYK2), site Thr495 by protein kinase C (PKC) [2, 36]. A negative regulatory site for phosphorylation is Thr495. Dephosphorylation of Thr495 is associated with stimuli such as histamine and bradykinine both elevating intracellular calcium concentration. Dephosphorylation of Thr495 has also been shown to favour eNOS uncoupling [9, 37]. In addition, phosphorylation of eNOS at Ser615/Ser633 increases eNOS calcium sensitivity and activity, while Tyr657 phosphorylation is associated with downregulation of eNOS activity. On the oxygenase domain, Tyr81 is phosphorylated by pp60src kinase and activates the enzyme while Ser114 is phosphorylated by ERK decreasing the enzymatic activity and NO production [2, 38].

Several other proteins also interact with eNOS and regulate its activity, such as: caveolin, heat shock protein 90 or eNOS interacting proteins, demonstrating the complexity of regulation of the eNOS activity [35, 37]. In addition, studies had shown shear stress and exercise training enhance eNOS gene expression in the aortic endothelium [9, 11]. This exercise training- induced increase in NO synthesis could contribute to reduced bioavailability of NO in cardiovascular diseases. This has led to the identification of consensus sites on the eNOS gene for regulation by numerous stimuli.

5 Nitric Oxide Signaling in the Cardiovascular System: Health And Disease

The main physiological effects of eNOS/nNOS-derived NO in the heart include a number of functional changes such as a reduction of the contractile frequency of cardiomyocytes and increasing distensibility of cardiomyocytes, and improvement of the efficiency of myocardial oxygen consumption, among others [39, 40]. Currently, differences in the subcellular localization of NOS in heart NO generation indicate that these enzymes exerts distinct roles in cardiac function [1]. However, compartmentalization of NOS seems to be a dynamic process as a cause or consequence of disease states [41].

It is known that all three NOS isoforms are a source of endogenous NO in the heart [1, 2, 42]. A putative mtNOS also is found in cardiac mitochondria but is still a controversial issue [40]. Both eNOS and nNOS are constitutively expressed in cardiac myocytes, which are essential for cardiac excitation-contraction coupling [4]. In cardiac myocytes, eNOS is co-localized in the caveolae of the plasma membrane bound to caveolin-3 [43, 44] differently from endothelial cells whereas interaction of eNOS with caveolin-1 is prominent [44].

NO is able to promotes its function *via* cGMP-dependent or independent pathways modulating function of downstream proteins *via* specific post-translational modifications, such as phosphorylation by PKG or S-nitrosylation [39, 45, 46]. NO exerts several and distinct effects on cardiac function and basal contractile function is influenced by the amount of NO (both exogenous and endogenous) whereas at low (submicromolar) concentration, there seems to be a small positive inotropic effect while higher (micromolar or above) concentrations exert a negative inotropic effects [42, 47]. Importantly, spatial confinement of specific NO synthase isoforms regulates the cardiac contractility process, making possible NO signals to have independent, and even opposite effects on cardiac phenotype [43].

In this sense, eNOS co-localization together with β-adrenergic receptors and L-type Ca^{2+} channels allows eNOS-generated NO to be within diffusion distance of its molecular targets [42, 43] whereas NO (at higher NO concentration) stimulates sGC and leads to production of cGMP. In sequence, activation of cyclic-GMP-dependent protein kinase PKG directly phosphorylates L-type Ca^{2+} channels to inhibit their function, attenuating β- adrenergic effects. Besides, PKG can limit the sensitivity of troponin C to Ca^{2+} via the intervention of troponin I. Both effects are responsible for causing muscle relaxation [48–50]. On the other hand, NO (at low concentration) can stimulate AC, formation of cAMP, and subsequent protein PKA-dependent phosphorylation of voltage-operated L-type Ca^{2+} channels (increasing intracellular Ca^{2+}), ryanoidine receptors (RYR), and phopholamban (while derepressing the sarcoplasmatic reticulum Ca^{2+}-ATPase (SERCA)) producing inotropic positive effects as well as phosphorylation of troponin I, therefore, increasing cardiomyocyte contraction [49, 50]. It is worth noting that, NO is also capable of signaling independent of cGMP *via* post-translational modification of protein thiol groups, referred to as S-nytrosylation that can occurs on cystein residues of proteins,

allowing amplification of NO signaling. S-nytrosylation can alter protein function in cardiac cells mostly by redox-dependent process [46].

In response to stimulus such as insulin or stretch, the eNOS activity in cardiomyocytes can be phosphorylated at serine 1177 (for human) and 1179 (for bovine eNOS); this phosphorylation is achieved by activation of PI3-kinase and Akt. In contrast, phosphorylation at the threonine residue 495 by AMPK or PKC can inactivate eNOS [51, 52].

The second isoform, nNOS, is located in the sarcoplasmic reticulum (SR), mitochondria, plasma membrane [53] and interacts mostly with RyR and xanthine oxidoreductase (XOR) [53, 54], and in a less degree, it is found in sarcolemmal membrane [41]. nNOS facilitates cardiac relaxation and modulates contraction. However, NO produced by nNOS stimulates SR calcium release, ultimately aiding in β-adrenergic stimulation [2]. In the healthy heart, nNOS-derived NO attenuates basal cardiac inotropy by modulating the activities of L-type Ca^{2+} channel (LTCC) in the plasma membrane to reduce the amplitude of intracellular Ca^{2+} transients through *S*-nitrosylation of RyR receptor 2 increasing SR calcium release or cGMP-dependent mechanisms [2, 53]. By contrast, the activity of the cardiac Na^{+}–Ca^{2+} exchanger is unaffected [53].

NO from constitutive nNOS can stimulating Ca^{2+} reuptake through SERCA. SERCA can be activated, which facilities myocyte relaxation. This process is cGMP/PKG independent and occurs by increasing PKA-dependent PLN phosphorilation at ser16 (PLN-Ser^{16}) and CaMKII-dependent PLN phosphorilation at threonine17 (PLN-Thr^{17}) [53, 55]. It has been shown that nNOS is increased in cardiac disorders such as in infarct, ischemia-reperfusion injury, hypertrophy and heart failure [53]. In this line, Jin et al. [56] showed that acute angiotensin II (Ang II, 1 μM) treatment to isolated left ventricular myocytes in vitro increases both mRNA/protein expressions and activity of nNOS. However, it was followed by a reduced NADPH oxidase production of superoxide, which moderates the levels of intracellular superoxide and ROS, and facilitate LV myocyte relaxation. In vivo, nNOS also was increased in LV myocytes from AngII-induced early hypertensive rats [56]. Thus, seems that an early event following pathogenic insult and during disease progression, nNOS plays protective roles in the heart under stress [53].

The third isoform, iNOS, is only expressed in the heart under stress or stimulated by inflammatory mediators, such as TNF-α or other pathophysiological stimuli such as atherosclerosis [2]. In fact, iNOS has been shown to be present during pathophysiological conditions of the myocardium [57–59]. Other observations indicate that iNOS expression remarkably increases the intracellular concentration of NO in cardiomyocytes, leading to an inhibition of myocardial contraction, which suggest that iNOS expression is strongly involved in the development of contractile dysfunction [45]. Other studies associate the involvement of iNOS in cardiac hypoxia and ischemia but still are conflicting. However, data from Strijdom's laboratory [42] suggest that iNOS as one of the source of increased NO levels in hypoxic cardiomyocytes (but not in microvasulcar endothelial cells). As highlighted by [42], in study with $eNOS^{-/-}$ mouse hearts [60], iNOS induction was greatly increased during

ischemia-reperfusion (possibly due to an adaptive mechanism) whereas elevated NO levels were associated with cardioprotection.

Therefore, abnormalities in NO signaling are linked with several disorders including hypertension, hypercholesterolemia, diabetes mellitus and atherosclerosis [4]. Hence, we will report below some diseases/disorders involving important changes in NO signaling, therefore, altering cardiovascular homeostasis.

Atherosclerosis – Endothelial Dysfunction Under physiological conditions, NO is essential for maintenance of the vascular wall in a quiescent state by inhibition of inflammation, cellular proliferation, and thrombosis [61].

In contrast, endothelial activation or dysfunction it is characterized by a shift from a quiescent phenotype to one that is activated both by defense mechanisms (physiological context) as in response to cardiovascular disorders (pathological context), mainly by redox signaling activation. This way, this process contributes to the expression of chemokines, cytokines and adhesion molecules in endothelium that are able to communicate with leukocytes and platelets and target inflammation to specific regions of body to clear microorganisms [61]. Oxidant-stress-induced disruption of endothelium-dependent vasodilation is involved in the pathogenesis of atherosclerosis and other cardiovascular diseases [61, 62].

Atherosclerosis is a major cause of mortality around the world and is an inflammatory disease in which the immune mechanisms interact with metabolic risk factors to initiate, propagate and activate lesions in the arterial tree [62, 63]. Conventional cardiovascular risk factors such as hypercholesterolemia, diabetes, smoking and hypertension can account for 80% of increased risk of coronary artery disease [63]. In atherosclerotic arteries, however, endothelial dysfunction contributes to myocardial ischemia [61]. The common feature of endothelial dysfunction is a decrease in the amount of NO bioavailable, which is detected as a decrease in endothelium-dependent vasodilatation [64]. There are many inhibitors of biological activity of NO including decreased L-arginine uptake, decreased co-factors (Ca^{2+}, calmodulin, BH4), inhibition of electron flow (NADPH), flavins), inhibition of NOS expression and inhibition of substrate binding to NOS and NO scavengers [64, 65].

As briefly mentioned earlier, in the physiological process of NO synthesis, functional eNOS transfers electrons from NADPH, via the flavins FAD and FMN to the haem, where the substrate L-arginine is oxidized to L-citrulline and NO [9]. NO NADPH-oxidase-derived O_2^- reacts with eNOS-derived NO to form the potent $ONOO^-$. However, in BH4 deficiency, oxygen reduction uncouples from NO synthesis, thereby converting NOS to a superoxide-producing enzyme in instead NO [66].

Oxidative depletion of BH_4 to BH_2, increased levels of asymmetric dimethylarginine (ADMA) of eNOS and S-glutathionylation, for example, have been associated with endothelial dysfunction through eNOS uncopling [66, 67]. In this line, Li et al. [195] found that disturbed flow produced by partial carotid ligation decreases BH_4 levels in C57bl/6 mice. In a next study, Li et al. [68], using a model of atherosclerosis in mice, showed that these perturbations of BH_4 homeostasis lead to an NOS uncoupling [68]. It was characterized by increased vascular superoxide

production and altered vascular reactivity, infiltration of T cells and macrophages, and an increase in cytokine production. In contrast, oral BH4 supplementation prevented NOS uncoupling and improved endothelial function in the carotid exposed to disturbed flow. The dissociation of eNOS has now been identified an important contributor to endothelial dysfunction and atherosclerosis. Thus, these studies suggested that reversal of eNOS decoupling may represent a viable strategy for the prevention or treatment of cardiovascular disorders.

Still in this line, in a recent study [69], transgenic mice developed with increased BH4 synthesis in cardiac myocytes and wild-type mice (with maintained nitric oxide synthase coupling) were submitted to transverse aortic constriction (TAC)-induced pressure overload. Surprisingly, it was found that constriction induced abnormalities in cardiac morphology and function similarly in both groups. However, oral BH4 supplementation was able to improve it. These results suggest that BH4 protects against heart disease independent of myocardial NOS coupling. Instead, its benefits were mediated by a protective effect coupled to multiple inflammatory cytokines, and attenuated infiltration of inflammatory macrophages into the heart. Therefore, the authors suggest that presence of inflammatory cascades may be a better predictor than NOS-coupling status in assessing the efficacy of exogenous BH4 therapy in humans. In view of this, BH4 has emerged as a possible therapeutic tool in cardiovascular/cardiometabolics disorders. However, more studies are needed to understand the mechanisms of action of this important molecule.

Hypertension The role of NO-cGMP signaling in vascular smooth muscle cells relaxation and the regulation of blood pressure is well characterized, both in humans and in animal models and increased evidence suggests that increased reactive oxygen species production, impaired NO signaling and reduced antioxidants bioavailability are involved in the pathogenesis of hypertension [70, 71].

In this context, genetic deletion of eNOS gene in mice ($eNO^{-/-}$) causes impaired endothelial dependent hyperpolarization-mediated relaxations associated with systemic hypertension [31]. Thus, Duplain et al. [72] evaluating eNOS and insulin in the regulation of glucose metabolism, showed that in addition to hypertension, $eNO^{-/-}$ mice were found to have metabolic insulin resistance and hyperlipidemia. In another study [73], a continuous supply of DNA construct containing the human eNOS gene was fused to the SHR rats and a single injection of the naked eNOS plasmid DNA was able to cause a significant reduction of systemic blood pressure for 5–6 weeks. Together, these findings denote a link between impaired NO bioavailability and hypertension, indicating a potential of using eNOS gene therapy for this disease, as well a potential mechanism linking metabolic and cardiovascular disease in humans.

NO antagonizes the effects of Ang II and downregulates the synthesis of angiotensin I-converting enzyme (ACE) in the endothelium as well as the expression of the Ang II type 1 receptor (AT1R) in vascular smooth muscle cells, attenuating both Ang II production as well as its downstream actions [74]. In contrast, Ang II decreases NO bioavailability by promoting oxidative stress [71, 74]. Thus, Mollnau et al. [75], in animal model, showed that Ang II infusion causes endothelial

dysfunction by increasing NAD(P)H oxidase-mediated vascular superoxide production, at least in part PKC-dependent. Besides, this increase in superoxide production promoted eNOS uncoupling, leading to impaired NO/cGMP signaling in this animal model. Thus, $O2^{-}$ generation and the eNOS uncoupling seem to be a consequence of PKC activity, suggesting that it activation can be involved in the induction of oxidative stress in hypertension [76]. In hypertension associated with obesity or diabetes, reactive oxygen species may favour activation of pro-inflammatory NF-κB-dependent reactive oxygen species generated by NADPH oxidases and other sources leading to increased NF-κB activity followed by eNOS and iNOS up-regulation [40].

Myocardial Infarction and Ischemia-Reperfusion Myocardial infarction (MI) is a disorder in which cardiac myocytes undergo necrosis as a consequence of interrupted coronary blood flow. Therefore MI is caused by coronary atherosclerosis and/or arteriosclerosis [77]. Left ventricle remodeling after MI is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors ischemic heart disease, develops adaptive response to myocardial ischemia, which ameliorates the function of the damaged heart [78]. Evidence shows the important role of NO in this process.

In fact, studies have shown a relationship between increased levels of iNOS in the myocardium of patients with heart failure and after MI [58, 59, 79]. In this sense, in $iNOS^{-/-}$ mutant mice submitted to MI, it was observed 5 days after MI that myocardial iNOS mRNA expression, plasma nitrate and nitrite concentration were significantly increased, which was associated with increased mortality [59]. Besides, after ischemia induced by coronary occlusion, followed by 24 h of reperfusion, iNOS knockout mice had a marked structural left ventricle remodeling decrease, a global cardiac function improvement, a transient attenuation of contractile dysfunction in some border zone sectors and a reduction in circumferential extent of wall thinning compared with control animals. These differences are evident as early as 7 days after MI [80]. Therefore, these findings suggest that increased NO production from iNOS expression contributes to MI and mortality.

Scherrer-Crosbie et al. [81] using $NOS3^{-/-}$ mice showed that presence of eNOS limits left ventricle dysfunction and remodeling in a murine model 1 month after MI in part by decreasing myocyte hypertrophy in the remote myocardium. In this line that eNOS deficiency is associated to maladaptive myocardium remodeling, in another study performed in eNOS-transgenic mice Janssens et al. [82], found 4 weeks after MI, that cardiomyocyte-restricted eNOS overexpression in fact limits cardiac dysfunction and remodeling, in part by decreasing myocyte hypertrophy observed noninfarcted myocardium.

However, although eNOS seems to prevent the progression of MI, it has been reported that neither genetic disruption of eNOS nor pharmacologic inhibition of eNOS activity alone induces MI in mice [77]. Conversely, complete genetic disruption of all three NOS isoforms promotes spontaneous MI in these animals which is associated with metabolic disorders and vascular alterations [77]. It is speculated that is due to some compensatory mechanism by other NO isoforms. Therefore,

these findings may provide a strong and useful tool to a better understanding of the significance of the defective NOS system in the pathogenesis of spontaneous MI [77] and associated disorders.

In front of all this, is clear that NO exerts essential role in cardiovascular homeostasis and a deregulation in its signaling by its isoforms changes are associated with several physiological and pathophysiological processes. Importantly, differences in the subcellular localization of NOS in heart result in distinct roles of these enzymes in cardiac diseases. This indicate a promising for new investigations in this field, targeting not only pharmacological as well as non-pharmacological therapies to increase NO signaling and bioavailability in cardiovascular system, as will be discussed in another section of this chapter.

6 Exercise Training and Nitric Oxide Signaling

The exercise training (ET) promote numerous beneficial cardiometabolic adaptations, being considered as a powerful non-pharmacological tool in the treatment of cardiovascular diseases. In this way, it is able to prevent or reduces vascular disturbs, inducing high NO production and low oxidative stress, as well as it is able to stimulate the production of other vasoactive substances that contributes for functional and structural vascular changes, reducing the peripheral vascular resistance and blood pressure. In addition, ET is able to promote angiogenesis mediated by VEGF and NO [83], decreases the Ang-II production and NADPH oxidase expression, resulting in a decreased eNOS uncoupling [84–86]. At the heart, the ET induces physiological cardiac hypertrophy, reduces the heart rate, reduces the sympathetic nervous system activity, and the systolic, media and diastolic blood pressure [87–89]. Also, the ET promotes important metabolic adaptations that reflects in the blood pressure control, such as reduction of plasma triglycerides and low density lipoprotein, as well as improves the insulin sensibility in tissues [90].

NO is the ultimate mediator of angiogenesis stimulated by VEGF, the main factor involved in vasculogenesis and angiogenesis. VEGF is an important exercise-induced endothelial growth factor. This factor is recognized as a key regulatory protein of physiological angiogenesis. It also functions as a potent anti-apoptotic factor for endothelial cells. In addition, VEGF induces the expression of anti-apoptotic proteins in endothelial cells, greatly assisting the formation of capillaries while inhibiting processes involving their loss. The mechanisms controlling the angiogenic process depend on a balance of proteins that regulate apoptosis. Exercise-mediated activation of VEGF and eNOS plays an important role in the control of cell survival because they are directly involved in the regulation of apoptotic proteins, showing the importance of these factors in the promotion of vascular homeostasis [12, 91]. In this way, Silva et al. [91] showed an increase in cardiac angiogenesis in trained rats following the protocol of swimming training of 1 h/day, 5 d/week for 10 weeks, with a load of 5% of the corporal load. This study concluded that ET promoted increased expression of miR-126 and that this may be related to cardiac

angiogenesis by indirect regulation of the VEGF pathway and direct regulation of targets that converged in an increase in angiogenic pathways, such as MAPK and PI3K/Akt/eNOS.

The NO also has been shown to be important for vascular tone at rest and during exercise. It is suggested that a compensatory form of prostanoids (20-carbon fatty acids synthesized via the cyclooxygenase (COX) pathway of the arachidonic acid cascade) and EDHF (endothelial hyperpolarizing factor) ensures that adequate blood flow is achieved when NO is impaired. These studies show an important role of NO in the regulation of exercise hyperemia [92–96].

ET promotes stimuli such as the physical force that blood exerts on the inner part of the vessel wall, this force is known as shear stress, which is transmitted to the vascular wall and the endothelium acts as a mechanical transducer, thus increasing the vasodilator mechanisms, such as NO, to normalize the high shear stress [11].

The mechanical effect of ET on the endothelium may be one of the explanations for increased NO up-regulation and production of eNOS. This release is induced by substances within the skeletal muscle such as ATP and adenosine, which are known as endothelial NO-forming stimulators [96, 97]. In addition, ET also has positive participation in the elimination of reactive oxygen species, which eliminate NO. NADPH oxidase is the main source in increasing reactive oxygen species production, thus, the half-life of eNOS is significantly shortened by the increase in $ONOO^-$ generation in the presence of oxidative stress, which is a key factor in endothelial dysfunction; however, it has already been demonstrated that ET may decrease the expression of NADPH oxidase [85, 98, 99].

eNOS can also produce reactive oxygen species in the vascular system. Some diseases may present an enzymatic reduction of molecular oxygen by eNOS, due to which it is not coupled with the oxidation of L-arginine, thus resulting in the production of superoxide instead of NO. The eNOS decoupling motifs are BH4, which is a cofactor of NO synthesis, the shortage of L-arginine, which also participates in the synthesis of NO, or even high levels of ADMA, an endogenous NO synthase inhibitor [100].

Studies have related the beneficial effects of ET in hypertensive patients to an improvement in the significant redox status. As already mentioned, ET improves endothelial function, cardiovascular control and improves endothelium-dependent relaxation. This endothelial adaptation is mainly mediated by the increase in NO production and the changes that ET causes in shear stress. ET also plays an expressive role in normalizing proinflammatory cytokine levels preventing decrease NO bioavailability [101, 102].

The endothelial adaptation exerted by the ET is important, therefore, it has a systemic effect of the redox state throughout the body, including the less exercising vascular beds when in physical activity [103]. Thus, ET was already associated with increased antioxidant levels and consequently with eNOS phosphorylation. A study [104] with wild-type (WT) mice and AMPKα2- knockout ($AMPK\alpha2^{-/-}$) mice, which the ET protocol for the trained group was ran on the treadmill for 90 min/day at 9.0 meters/min (0% grade), 5 days/week for 6 weeks, investigated whether ET had any beneficial effect on vasodilation and identified that exercised WTs exhibited

increased protein expression and eNOS phosphorylation in the aorta compared to non-ET WT mice, whereas exercised knockout mice showed no difference in their control group. Therefore, these results indicate that improved vasodilation in the aortas during training in mice may be through an AMPKα2-dependent mechanism. This study concluded that exercise improved endothelial and mitochondrial function of the aorta through the activation of AMPKα2, which is involved in NO-dependent vasodilation, and suggests that AMPKα2 along with NO may play a critical role in exercise-related improvement of function vascular in disease such as hypertension.

It is well established that ET decreases blood pressure and improves endothelium-dependent vasodilation in patients with hypertension; this is done by increasing NO bioavailability in the vascular wall. These studies suggest that regular aerobic physical exercise is beneficial in maintaining resistance to oxidative stress and should be considered as an essential part of the patient's treatment [14, 101]. Roque et al. [14] demonstrated that ET reduced vascular stiffness of the coronary and mesenteric arteries of SHR. These responses are associated with reduced collagen deposition and superoxide production along increased antioxidants levels and NO bioavailability. These results demonstrate the beneficial effect of ET on decreasing blood pressure in hypertensive rats.

In an study of Claudio et al. [105] had as objective evaluate the effects of ET on endothelium-dependent coronary vasodilation in ovariectomized hypertensive rats (SHRo). The ET protocol was 5 times/week, 60 min/day of swimming that for 8 weeks. The vasodilator response was measured in hearts in the absence and presence of a L-NAME. Vasodilation in SHRo was significantly reduced, even in the presence of L-NAME, and there was an increase in oxidative stress. These effects were prevented by ET and were associated with a decrease in oxidative stress. In conclusion, swimming ET prevented endothelial dysfunction in the SHRo coronary bed associated with an increase in the expression of antioxidant enzymes and, therefore, may prevent coronary disease in postmenopausal hypertensive women.

Chronic heart failure (CHF) impairs the regulation mediated by NO of skeletal muscle; this deterioration in NO-mediated function plays an important role in the hyperemic response characteristic of CHF. This hyperemia results from the reduction of venous drainage, which causes distension distal veins, venules and capillaries [106]. This contributes to pathological PO2mv (microvascular muscle oxygenation) profiles, which means that the accelerated kinetics of PO2mv. However, ET can be used as a non-pharmacological treatment to improve NO-mediated function in skeletal muscle in CHF individuals, ET contributes to a decrease in muscular PO2mv kinetics [107–109].

In an study of Hirai et al. [110] tested the hypothesis that ET would improve microvascular oxygenation of muscles in CHF rats mediated by enhanced NO function. A progressive load aerobic ET was used, 5 days/week for 6–8 weeks. The trained CHF rats had a higher peak oxygen uptake, the decrease velocity of PO2mv was reduced, that is, a slower kinetics, improving the oxygenation of microvessels, compared to its control group. Also, Linke et al. [107] showed CHF patients trained by 4 weeks on a ergometer bicycle had an improvement in vasodilator capacity. In

addition, Hambrecht et al. [111] used 3 weeks of aerobic ET in a CHF patient to determine the systemic effects of ET on endothelium-mediated vasodilation. After exercise, blood flow significantly improved in response to acetylcholine and there was an increase in peak oxygen uptake related to endothelium-dependent change in peripheral blood flow, concluding that ET improves basal NO formation and endothelium-dependent vasodilation.

In coronary artery disease (CAD), the endothelium produces less NO and with this reduction a decrease in tissue perfusion, causing a thrombus formation. This decrease in NO level can be caused by oxidized superoxide anions and low-density lipoproteins (LDLs-ox). These in turn deactivate the endothelial receptors for acetylcholine, VEGF, serotonin, thrombin, bradykinin, thereby decreasing the stimulation of NOS in endothelial cells and, consequently, reducing NO production, impairing relaxation of smooth muscle cells and predisposing to formation atherosclerotic plaque [112].

In study of Hambrecht et al. [111] which aimed to investigate the effect of ET on endothelial function in relation to eNOS and its Akt-dependent phosphorylation (protein kinase, plays a role in the intracellular signaling pathway for protein synthesis) in patients with stable CAD. In this study, the relationship between Akt phosphorylation and and phospho-eNOS levels and mean peak flow velocity, was confirmed that ET has beneficial effects on endothelial dysfunction in patients with CAD and this effect is related to increased exercise-induced shear stress and increased Akt dependent on eNOS phosphorylation at position Ser1177 (human sequence).

As previously mentioned, ET leads to the regulation of anti-oxidative defense mechanisms, studies have shown that this helps to reduce oxidative stress after cardiac ischemia or reperfusion, with the increase of the antioxidant capacity of the exercise there was a prevention of excessive synthesis of NO, limiting its binding to O_2 and consequent formation of $ONOO^-$ [113]. During the cardiac ischemia and reperfusion process, there is significant cardiac dysfunction and myocardial apoptosis.

A study of Zhang et al. [114] which followed a swimming protocol of 3 h/day, 5 d/week for 8 weeks, exercise resulted in decreased apoptosis and improved cardiac function by enhancing expression of AKT, AKT phosphorylation, and glycogen synthase kinase (GSK)-3β. Treatment with a PI3K inhibitor abolished the beneficial effects of exercise, providing a mechanistic understanding of the effects of exercise on apoptosis and cardiac function. Exercise also induces endothelial progenitor cells to promote angiogenesis. The growth of new blood vessels is an important natural process needed to heal wounds and restore blood flow to tissues after ischemia and cardiac reperfusion injury [115].

The modulation of atherosclerosis disease may be by the expression of adhesion molecules, that is, the binding of leukocytes to the vascular endothelium, which may form cholesterol-laden macrophages, causing the smooth muscle cells to proliferate and migrate into the subentothelium and form platelet aggregation, forming blood clots. Leukocyte adhesion is promoted by the expression of the P-selectin and VCAM-1 (vascular cell adhesion molecule-1) [116, 117].

Indolfi et al. [118] studied the impact of ET on atherosclerosis. They simulated angioplasty of the rats carotid artery, which the vessel wall injury causing a neointima formation to verify vascular remodeling. The animals were divided into trained injured and only injured group. It was found that in the trained animals there was a great decrease in the proliferation and migration of the smooth muscle cells, therefore, there was a decrease in neointimal hyperplasia in the injured artery. It also had a positive result in increasing eNOS expression and activity in trained animals.

NO protects the vascular wall by inhibiting platelet aggregation, penetrating white blood cells into the media and intima layers and by lipid oxidation, so NO can attenuate atherosclerosis protecting the vessel. ET increases the bioavailability of NO by: increases the amount and activity of eNOS, increases the availability of the eNOS substrate that is L-arginine, and also increases the essential cofactors (BH4) mentioned above, decreases decomposition of NO by ROS and shear stress is one of the main activators of mRNA and eNOS proteins in ET [119, 120].

Richter et al. [121] evaluated whether the ET of endurance, which has its cardioprotective characteristic, could beneficially affect risk markers in atherosclerosis, ADMA, myeloperoxidase (MPO), and paraoxonase 1 (PON1), which act by the modulation of oxidative stress/NO bioavailability. Individuals with cardiovascular risk and CAD were used. The training consisted of 12 weeks of ET. It was found that serum levels of ADMA and MPO were significantly reduced after ET. Downregulation of ADMA and MPO was inversely correlated with plasma levels of cGMP, this was reflected in NO production. This study proved that ET is beneficial in the regulation of ADMA and MPO, risk markers. Therefore, ET can be used as a non-pharmacological treatment against atherosclerosis due to improvement in NO bioavailability, through increased availability of L-arginine, a reduction of oxidative stress and lipid peroxidation.

In conclusion, all this data suggest that NO is increased in ET by several pathways and it is related to beneficial effects on cardiovascular diseases, mainly by vascular function regulation (Fig. 13.3). Taken together, ET may increase the bioavailability of NO. The increased stress shear in exercise promotes the synthesis of BH4, which in turn increases eNOS activity. ET also decreases the expression and activity of the NADPH oxidase, thus being effective as an antioxidant therapy. It also prevents platelet aggregation, in which it is inhibited by increased cGMP-mediated NO, positively affecting atherosclerotic plaque. With improved NO function, exercise promotes a beneficial effect on microvascular remodeling, decreased proliferation and migration of smooth muscle cells, thus avoiding large neointimal hyperplasia and inducing angiogenesis; making ET a great ally in the treatment of cardiovascular diseases.

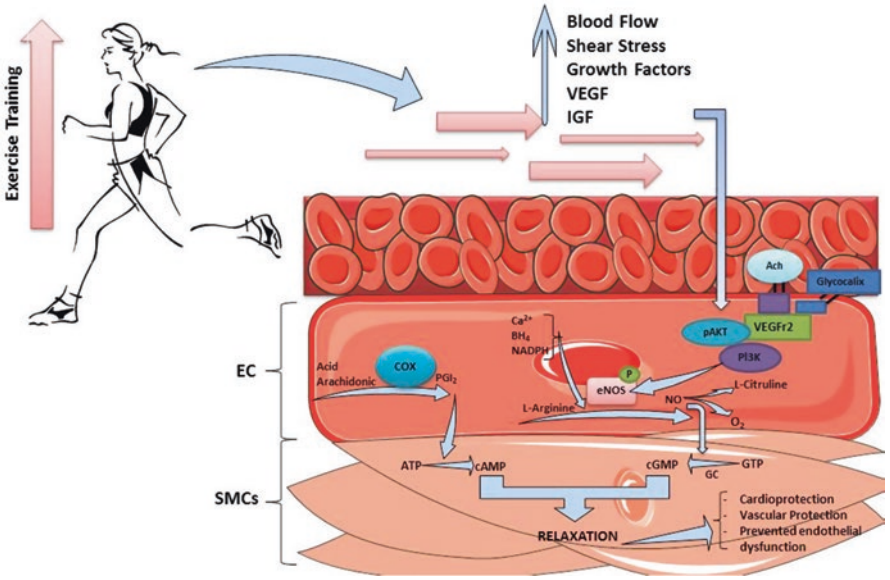

Fig. 13.3 The effects of ET on the vascular endothelium are mediated by increases in shear stress (In the vascular lumen, due to increased exercise, acetylcholine (Ach) signaling occurs in endothelial cells (EC) and glycocalix deformation may also occur through glycocalyx activating phospholipase activity, due to an increase in intracellular release Ca^{2+}, prostaglandin I2 (PGI2), and relaxation of smooth muscle cells (SMCs) that are mediated by cyclic adenosine monophosphate (cAMP). Vascular endothelial growth factor receptor 2 (VEGFR2) can activate phosphoinositide 3-kinase (PI3K) to phosphorylate protein kinase B (Akt) which induces AKT-mediated nitric oxide synthase endothelium (eNOS) phosphorylation, leading to increased production of NO. Guanosine-5′-triphosphate (GTP) is catalyzed by soluble guanylil cyclase (GC) in the 3′ , 5′-guanosine Monophosphate (cGMP), this in turn by SMCs produces relaxation by multiple contractile mechanisms *AA* Arachidonic acid, *COX* Cyclooxygenase, *ATP* adenosine triphosphate, *NADPH* nicotinamide adenine dinucleotide phosphate, *VEGF* vascular endothelial growth factor, *IGF* insulin growth factor)

7 MicroRNAs That Targets NO Pathway: Relations Between Exercise and Cardiovascular System

Considering all vascular and cardiometabolic benefits induced by ET and the genetic findings of the last decade, it becomes possible to discuss about miRs in the cardiovascular system. The miRs are a new class of posttranscriptional regulators of gene expression located in all body tissues, and today studied by many scientists around the world. As the miRs can acts into the cells of all organs to control the protein synthesis in all biological processes, also has been shown that many miRs can be regulated by ET into the blood vessels and heart, contributing to prevention or reduction of cardiovascular disturbs, as well as if in the presence of biological imbalances, may contributes to initiate or potentiate the development of diseases. Sometimes, the miRs are small, noncoding RNAs with 17–25 nucleotides in length,

which acts as potent posttranscriptional regulators of genes by coupling with sites in 3'untranslated (3′-UTR) in the messenger RNAs (mRNAs) of protein-coding genes and negatively regulates their expression [83, 122–124]. Initially, at nucleus the RNA polymerase II transcribes the primary miR (pri-miR), which is cleaved by the RNase III enzyme Drosha to form the pre-miR. After, the pre-miR is transported by exportin 5 from nucleus to the cytoplasm, where an RNase III enzyme process the pre-miR and create a oligonucleotide duplex, which is integrated into the RNA-induced silencing complex (RISC complex) and is selected a strand that is stripped to create the miR mature [125, 126]. After created, the miRs acts into the cytoplasm by complete or incomplete pairing at the 3′-UTR site of mRNAs, and associated to the fact of that it are small sequences of nucleotides, a single miR can regulate up more than two hundred mRNAs, and more than one miR can regulate a single mRNA, blocking the protein synthesis [83, 127]. In this way, considering the above-mentioned about miRs and cardiovascular system, the purpose of this section is to discuss about the miRs modulated by ET and its targets in the NO-synthesis pathway in cardiovascular system.

The NO is very well known as a molecule that exerts an importante role in the regulation of vascular contractile activity [128, 129], and its satisfactory bioavailability at the cardiovascular system may depends of the life style of subject. For sample, it is known that psychological stress may reduce the activity of endothelial NO synthase (eNOS) and the vascular NO production [128–131]. On the other hand, the ET may increases eNOS-derived NO vascular bioavailability [130, 131], may increases the left ventricle eNOS protein levels in rats [91], enhances myocardial perfusion by increasing both eNOS and extracellular superoxide dismutase expression, preventing the premature breakdown of NO by reactive oxygen species (ROS) [132] and improves the endothelial function in patients with coronary artery disease by increasing phosphorylation of eNOS [111]. Also, it is important to remember that ET increases the blood shear stress in the vessels wall, leading to upregulation of guanosine triphosphate cyclohydrolase/tetrahydrobiopterin pathway [133], which is essential of stabilizing eNOS [129].

Concerning about the miRs in the cardiovascular system, specific miRs are important to protect against the development of many diseases associated with NO metabolism, such as hypertension, atherosclerosis, pathological left ventricular hypertrophy, coronary artery disease, heart failure, myocardial infarct, intracranial aneurysm, stroke, brain infarction, carotid intimal-media thickening, venous thrombosis, peripheral vascular disease and others. In this way, many genes associated to the synthesis of NO may be target of miRs. About this, we show an overview of the current knowledge about individual miRs that acts on the pathway of NO synthesis and are modulated by ET.

miR-34a The miR-34a targets the silente information regulator 1 (SIRT1). This miR is related to endothelial progenitor cell senescence and blocks its angiogenesis [134]. It was shown that it suppress the cell proliferation by inhibits the cycle cell and impairs the endothelial progenitor cells-mediated angiogenesis via inhibiting SIRT1 [126, 135]. Sometimes, the arterial SIRT1 expression is reduced in older

rodents [136] and humans [137]. The SIRT1 exerts an important role in endothelial homeostasis because it dacetylates eNOS at lysine residues in the calmodulin-binding domain and then stimulates eNOS activity, increasing the NO production [100]. Mattagajasingh et al. [138] shown that SIRT1 induces endothelium-dependent vascular relaxation by activating eNOS, and that NO production can be decreased by siRNA-mediated SIRT1 knockdown. Considering this discussion, the ET is able to activate SIRT1 and eNOS in the mouse aorta [139] and also it is able to decelerate the deleterious effects of aging process via SIRT1-dependent pathways in aged rats [140]. About miRs, ET increased miR-34a blood stream of individuals who performed marathon, and this effect was associated to control of exercise-induced inflammatory cascade [141], but nothing related to the NO was shown. However, previous results of our laboratory, obtained from microRNA microarray shows that ET was able to decrease the miR-34a expression in aorta of trained rats compared to sedentary group, and that hypertension was able to increase the miR-34a expression in aorta of spontaneous hypertensive rats (SHR) compared to sedentary group. These results were associated with increased eNOS protein levels in aorta of trained rats compared to control and SHR groups. Besides, is was shown in heart rats that silencing of miR-34a attenuates cardiac dysfunction in a setting of moderate, but not severe, hypertrophic cardiomyopathy [142]. This study showed a relation between miR-34a and SIRT1 in heart, but without any discussion about eNOS. However, until now there is no study showing a direct link of the effects of ET on miR-34a and NO in heart.

miR-181a Such as miR-34a, the miR-181a directly target SIRT1, but not target directly eNOS. The high circulating levels of this miR are positively associated to hypertension, independent of circulating renin [143]. However, data of the microRNA microarray of our laboratory shows the ET also was able to decrease the miR-181a levels in aorta of trained compared to sedentary rats, and that hypertension in SHR was able to increase the levels of this miR compared to sedentary group. There are no yet published data in the literature associating ET, microRNA-181a and eNOS or NO production in cardiovascular system of humans until this moment. In the heart, [144], showed that swimming ET was able to down-regulate miR-181a in physiological cardiac hypertrophy.

miR-10b The 3'UTR of eNOS has not target sequence for miR-10b, but phosphatase and tensin homolog (PTEN) has target for this miR. In this way, the miR-10b can negatively regulates eNOS phosphorylation and NO production via PTEN, a negative regulator of the PI3K/Akt/eNOS pathway [145]. However, it is no have published data in the literature about the association of ET, microRNA-10b and eNOS until this moment. But data of the microRNA microarray of our laboratory (data not published) shows that ET promotes increase of the miR-10b levels in aorta of trained and decrease in aorta of SHR rats, both compared to the sedentary. Also, the ET promotes increase of eNOS protein expression in the trained group compared to sedentary.

miRs-221/222 These miRs are expressed in endothelial cells, but not only confined into them. In this way, it has been shown that these miRs can be upregulated in the circulation by exercise and may be used as biomarkers of ET [146]. It is probably that during ET the upregulation of this cluster may be related only to the exercise adaptations in response to increased shear stress, however with no promoting any serious problem to the cardiovascular system. However, it has been discussed that upregulation of the miRs-221/222 cluster in arterial endothelial cells may predispose the individual to the cardiovascular disease, since they are able to downregulate eNOS and inhibit angiogenesis [147]. It is knowed that NO synthesized by eNOS is essential to the vascular remodeling and angiogenesis (Suárez and Sessa [149]), but the overexpression of this cluster indirectly reduces the eNOS levels in Dicer siRNA-transfectecd cells [148], suggesting an indirect regulation of eNOS protein by miRs-221/222, since there are no direct target sequence in the eNOS mRNA for this cluster. Also, this cluster have anti-angiogenic action because these miRs may directly target c-kit, which is a tyrosine kinase receptor for stem-cell fator that induces capillary tube formation [149].

miR-21 This miR is expressed in vascular smooth muscle cells, endothelium, cardiomyocytes and fibroblasts [150]. It is downregulated in senescent human aortic endothelial cells and is able to regulate the proliferation cells by suppressing PTEN [151]. This miR is induced by shear stress and its high levels were detected in pulmonary hypertension [152], as well as in the circulation during ET [146]. As this miR is able to target superoxide dismutase 2 and PTEN, which is a negative regulator of eNOS, its increased circulating levels during ET may be related to the control of oxidative stress and to demand for NO in the angiogenesis post exercise. On the other hand, this miR also can directly target the Bcl-2 (B-cell lynphoma 2 protein), an anti-apoptotic protein. In this way, the high expression of miR-21 in soleus muscle and decreased expression of Bcl-2 were associated with hypertension by [12], who also showed that ET was able to reduce the miR-21 expression and normalize the capillary rarefaction in skeletal muscle of hypertensive rats. Also, the microRNA-21 is increased in left ventricle pressure overload, leading to the cardiac fibrosis via PTEN/Akt pathway regulation, stimulating an endothelial-to-mesenchimal transition (EndMT). Antagomir against microRNA-21 is able to suppress transforming growth factor-β (TGFβ)-induced EndMT [153], suggesting that this microRNA is a powerful target to treat pathological cardiac hypertrophy.

miR-22 The miR-22 is related to the control of physiological cardiac hypertrophy and also with the cardiac-myocyte protection during cardiac ischemia and reperfusion (I/R). The swimming ET is able to promotes down-regulation of miR-22 in physiological cardiac hypertrophy [144]. Although this miR can directly target SIRT1, which induces eNOS activity and NO production, the study of [144] gave no focus the eNOS-NO signaling in physiologically hypertrophied hearts. However, it was uncovered that the miR-22 is a critical regulator of cardiomyocyte hypertrophy and cardiac remodeling [154]. On the other hand, this miR is up-regulated during cardiac I/R, in which there is low NO bioavailability and high levels of ROS. Mechanistically, overexpression of miR-22 have few effect on cardiac eNOS

total, but this microRNA can binding at a site of the 3'UTR of caveolin-3 to down-regulate it during I/R, thus restoring a deficiency of eNOS activity and NO bioavailability [155], minimizing myocyte apoptosis and cardiac injuries induced by ROS.

miR-155 The miR-155 is expressed in endothelial cells, smooth muscle cells, and also in macrophages. This miR can be induced by shear stress [156] and it is upregulated in human atherosclerosis [157]. It can targets the angiotensin-II type-1 receptor and endothelin 1, both involved in hypertension. However, [158] showed that it also can directly target eNOS mRNA 3'UTR, decreasing eNOS and NO bioavailability. Considering ET and vascular system, [159] showed that treadmill exercise was able to down-regulate microRNA-155 in aorta of male ApoE null C57BL/6 J mice. In this way, the microRNA microarray carried out in our laboratory also showed that ET was able to down-regulate microRNA-155 in thoracic aorta of trained rats that swimming for 10 weeks, 60 min per day, and 5 days/week compared to the sedentary rats (data not shown). The association of ET, microRNA-155 and eNOS in cardiovascular system has not been shown in literature until moment.

miR-126 The miR-126 is an endothelial-specific microRNA that is involved in angiogenesis and vascular integrity. It is able to modulate the VEGF pathway by directly target sprouty-related protein 1 (spred-1) and phosphatidyl-inositol 3-kinase regulatory subunit 2 (PI3KR2), a negative regulator of angiogenesis. Through this mechanism, it may indirectly modulates the PI3K/Akt/eNOS pathway [160]. Concerning about association of ET, miR-126 and eNOS, it was showed by [91] that swimming ET was able to up-regulate miR-126 in physiologically hypertrophied heart rats, to decrease PI3KR2 mRNA expression, to increase phosphatidyl-inositol 3-kinase (PI3K) protein expression, to increase phosphorylated Akt and phosphorylated eNOS proteins compared to sedentary rats.

Other miRs Other cardiovascular miR that target SIRT1 is the miR-217, which induces endothelial cell senescence and reduces the NO availability [161]. Also, it has been shown that miR-133a is a potential therapeutic target for preventing cardiovascular diseases. The inhibition of aberrant miR-133a expression in endothelial cells prevents endothelial dysfunction by targeting GTP cyclohydrolase 1, reducing the uncoupling of eNOS [162]. Still, the miR-92a can indirectly suppress the eNOS expression by targeting Kruppel like factor 2 (KLF2), which is knowed as an inductor of eNOS expression and atheroprotector [196]. MiR-103/107 have been shown to target caveolin-1 to downregulate its expression. Caveolin-1 is a tonic inhibitor of eNOS activity [163]. However, no association among ET, bioavailability of NO, and miRs: -217, -133a, -92a and -103/107 in the cardiovascular system has been studied until now. This is an open field for new discoveries.

The Fig. 13.4 shows a schematic summary of association among ET and cardiovascular miRs that targets the pathway of NO synthesis.

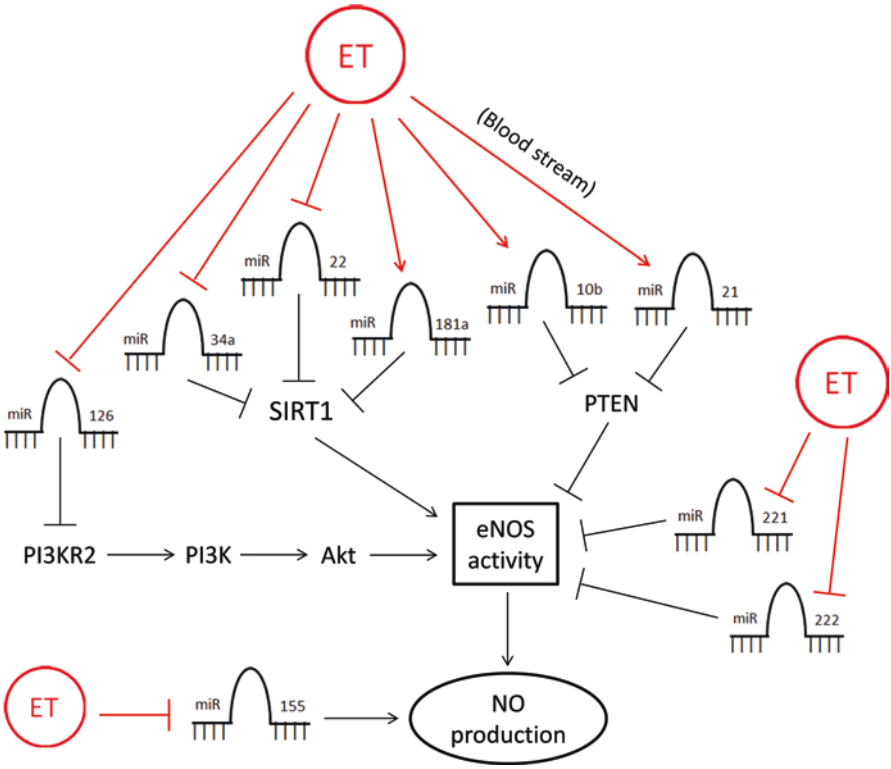

Fig. 13.4 Schematic summary of association among ET and cardiovascular miRs that targets the pathway of NO synthesis (*ET* exercise training, *miR* microRNA, *SIRT1* silente information regulator 1, *PTEN* phosphatase and tensin homolog, *PI3KR2* phosphatidyl-inositol 3-kinase regulatory subunit 2, *PI3K* phosphatidyl-inositol 3-kinase, *Akt* phosphorylated serine/threonine kinase 1, *eNOS* endothelial nitric oxide synthase, *NO* nitric oxide)

8 Nitric Oxide as Target for Development of New Therapies

During the last decade, NO has been used as new procedures of therapies to treat diseases or improving ability of certain life needs. However, exogenous NO delivery can produce different effects on cardiovascular system by affecting the NO signaling pathways. In fact, high concentrations of NO are regarded as cytotoxic, as extra production or delivery of NO may lead to the production of the highly reactive $ONOO^-$ anions, which affect essential cellular components and eventually set on the mechanisms leading to cell death [1, 2, 27]. Therefore, NO-based therapies are becoming approachable and with more investigation have the potential of developing into beneficial therapeutic approaches for cardiovascular and other diseases in the future [1, 8, 10, 164].

Endothelial dysfunction is often noted in patients with atherosclerotic risk factors and cardiovascular diseases; antecedent exposure to various risk factors disables

endothelial cells to produce sufficient amount of NO, leading to the first step toward inflammatory responses and atherosclerosis [8, 164]. Studies have demonstrated that administration of L-arginine to human with risk factors for atherosclerosis or with pre-existing lesions can enhance endothelium-dependent vasodilatation [165, 166]. The authors observed that oral L-arginine administration attenuates platelet aggregation in hypercholesterolaemic humans. As in animal models, this is associated with increase in platelet cGMP, indicating that NO exerts its beneficial effects in cardiovascular diseases. It is most likely that hypercholesterolemia and other states engendering atherogenesis, induce an alteration in enzyme affinity or L-arginine availability. Indeed, elevated levels of endogenous NOS inhibitor has been described in certain disease states, like in uraemic and hypercholesrerolaemic patients. ADMA circulates in plasma concentrations and antagonize NOS inducing vasoconstriction in isolated vascular rings [167, 168]. Enzymes responsible for the synthesis and/or degradation of this circulating factor may be a target for drug development. Recently, Judkins et al. showed atherosclerotic lesion formation is strongly associated with increased NADPH oxidase activity and elevated expression of the superoxide-generating Nox2 isoform. The authors crossed hypercholesterolemic apolipoprotein E knockout ($ApoE^{-/-}$) mice with Nox2 knockout ($Nox2^{-/-}$) mice to generate a double-knockout strain (i.e. $Nox2^{-/-}/ApoE^{-/-}$). Compared to the single knockout $ApoE^{-/-}$ strain, $Nox2^{-/-}/ApoE^{-/-}$ mice maintained on a high-cholesterol diet displayed markedly reduced vascular superoxide production, augmented NO bioavailability, and were profoundly protected from the development of atherosclerotic lesions along the descending aorta [164, 169].

Coronary vasodilation, together with strategies to limit oxidative stress, is desirable in the treatment of stable angina. Organic nitrates, a class of nitrovasodilator, are effective anti-anginal agents with an ability to donate NO and vasodilate capacitance veins and conduit arteries leading to improved coronary blood flow and a reduction in cardiac work. Nitrates also prevent coronary vasospasm and inhibit platelet aggregation, beneficial actions in the maintenance of perfusion to the ischemic myocardium. Members of this drug class include glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN) and isosorbidemononitrate (ISMN), all of which are used clinically to alleviate the symptoms of angina. A major limitation of nitrates is their susceptibility to tolerance development and ability to cause endothelial dysfunction [164, 170]. Despite the potent blood pressure lowering effects of nitrovasodilators, they are currently only administered during acute hypertensive crises as chronic administration is prohibited by tolerance development, systemic hypotension and reflex tachycardia. In addition, NO donors may also be metabolized to $ONOO^-$ [164]. Curiously, chronic treatment with superoxide dismutase was highly effective at reducing blood pressure in spontaneously hypertensive, but not normotensive rats [171], suggesting oxidative stress is a key contributor to compromised NO function in vascular and cardiac pathologies [172] and there has been much interest in the development of therapeutics which limit or prevent oxidative stress [8, 164, 173]. In this way, numerous clinical trials of antioxidants have been conducted [8]. Contrary to thousands of in vitro and animal studies and acute beneficial effects on endothelial functions in humans [174], the results of systemic and

long-term administrations of antioxidants have been disappointing in many clinical trials. Indeed, long-term antioxidant therapy for patients with hypertension failed to lower systemic blood pressure or to improve mortality rate [175, 176]. A supplementation of BH4, an essential co-factor for NOSs to produce NO, was neutral [177], and an iNOS inhibitor increased the mortality rate in patients with septic shock [8, 178]. The poor efficacy of antioxidants may be due to their: inability to neutralize all ROS and outcompete the interaction of ROS with NO, oxidation per se and/or interaction with ROS to generate another oxidizing compound [164].

Recently, NO has been implicated in the mechanisms responsible for limits myocardial ischemia-reperfusion (I-R) injury [164]. Exogenous NO donors limit infarct size and plasma cardiac enzyme levels, when added at the onset of reperfusion, often accompanied by improved post-ischemic recovery of coronary blood flow, in large animal models of I-R [179]. In patients, the nitrosovasodilator glyceryltrinitrate (the only NO donor available for short-term use in human), administered i.v. <4 h after the onset of chest pain, reduces infarct size and improves cardiac function post infarction [180]. Mechanisms attributed to the cardioprotective actions include variable contributions from sGC/cGMP (often secondary to improved coronary perfusion), S-nitrosylation, K^+ channels and antioxidant mechanisms [164].

Recently, it has been approved that NO is highly effective pulmonary vasodilator for newborn infants with persistent pulmonary hypertension of the newborn or hypoxemic respiratory failure [181, 182]. NO has been used for treating pulmonary hypertension [183]. Ochikubo with others in 1997 [184] applied inhalation therapy of NO gas on infants with severe persistent pulmonary hypertension. They found that the pulmonary blood flow and oxygenation were increased. In addition, there were improvements in the systemic cardiopulmonary hemodynamics of the infants who inhaled NO. Also, the therapy by NO to reduce pulmonary vascular resistance were reported [185]. The effect of inhaled NO therapy on children with acute hypoxemic respiratory failure have been investigated by Dobyns with others in 1999 [186]. They reported that acute improvement in oxygenation in children with severe acute hypoxemic respiratory failure. Gas exchange in neonates can be improved by NO [187]. Lindberg and Rydgren have approved that pulmonary hypertension and hypoxemia can be treated by inhaling NO [188]. NO could be used in treating patients with seasonal allergic rhinitis to lower airway inflammation [189].

In case of heart failure, the reduction of NO bioavailability has been reported [190]. During the human growth hormone treatment, both L-arginine and NO levels decreased significantly [191]. However, NO can be increased directly or indirectly. Exercising and nutrition are considered to be the way to increase the NO levels. Using oral L-arginine or nitrite therapy were reported to increase the production of NO [190, 192, 193].

In 2016, Brolaug et al. [194] have found that the hemodynamic abnormalities in heart failure patients with preserved ejection fraction are associated with adverse outcomes, and are believed to be related in large part to deficits in NO availability. In the study, they showed acute administration of sodium nitrite (90 mg), which is converted to NO in vivo, reduces biventricular filling pressures and pulmonary

artery pressures at rest and during exercise with no changes in the cardiac output or the stroke volume [194]. Previously, the authors showed that intravenous nitrite substantially improves exercise hemodynamics and cardiac reserve in these patients. Thus, the inorganic nitrate–nitrite pathway represents a novel NO-providing therapy to improve clinical status in patients with heart failure or pulmonary hypertension.

Considering the limitations of clinically used nitrovasodilators and lack of efficacy of antioxidants in the treatment of cardiovascular disease, attention has turned to alternate NO- donating molecules including nitrates, nitrites and NO-metal complexes such as sodium nitroprusside. Indeed, other NO-related species such as nitroxyl (HNO) and S-nitrothiols have been effective as vaso-and cardio-protective agent with therapeutic advantages [1, 2, 8].

9 Conclusion

After the discovery of NO, many functions have been attributed to this mediator in the field of basic medical sciences and clinical cardiology. NO plays an important role in the regulation of cardiovascular functions in health and disease by, for example, promoting vasodilation, inhibiting vascular smooth muscle cell growth, platelet aggregation, and leukocyte adhesion, apart from by regulating myocardial function and providing cardioprotection; making it a fascinating molecule for study. Experts agree that NO is a potent and effective agent of cardioprotection, protecting the heart and blood vessels against cardiovascular disease. However, accumulation of excess NO contributes to an increased oxidative/nitrative stress, demonstrating that its bioavailability is tightly regulated by multiple fine-tuned mechanisms. Thus, the concentration of NO will determine its chemistry, the distance it diffuses, and the type of signaling targets it interacts with. In this way, the interaction of NO with reactive oxygen species determines the biological mechanisms of action and short half-life of NO, establishing the cellular phenotype. The impaired NO signaling in the heart due to the presence of risk factors and diseases leads to different pathophysiological processes including myocardial hypertrophy, fibrosis and eventually heart failure. Therefore, restoration of NO signaling in the heart by exercise training or pharmacological tools may be a promising therapeutic avenue to alleviate cardiac pathologies. In fact, exercise training practice may contribute to the long-term reduction of cardiovascular morbidity and mortality. Among the pharmacological agents, miRs target many genes associated to the synthesis of NO, emerging as an important therapeutic candidate for diseases. Understanding the NO molecular mechanisms of signaling pathways in the heart and vascular system can provide a new strategic approach to prevention and treatment of cardiovascular diseases.

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Chapter 14
C/EBPB-CITED4 in Exercised Heart

Shengguang Ding, Tianyi Gan, Meiyi Song, Qiying Dai, Haitao Huang, Yiming Xu, and Chongjun Zhong

Abstract C/EBPB is a crucial transcription factor, participating in a variety of biological processes including cell proliferation, differentiation and development. In the cardiovascular system, C/EBPB-CITED4 signaling is known as a signaling pathway mediating exercise-induced cardiac growth. After its exact role in exercised heart firstly reported in 2010, more and more evidence confirmed that. MicroRNA (e.g. miR-222) and many molecules (e.g. Alpha-lipoic acid) can regulate this pathway and then involve in the cardiac protection effect induced by endurance exercise training. In addition, in cardiac growth during pregnancy, C/EBPB is also a required regulator. This chapter will give an introduction of the C/EBPB-CITED4 signaling and the regulatory network based on this signaling pathway in exercised heart.

Keywords Exercise • Heart • C/EBPB • CITED4

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It has been well established that exercise has beneficial effects on heart [1, 2], though the underlying mechanism still requires to be investigated [3, 4]. A specific signaling pathway has gained interest recently. It works through the CCAAT/enhancer- binding protein B (C/EBPB, C/EBPβ) and CBP/p300-Interacting transactivators with E (glutamic acid)/D (aspartic acid)-rich-carboxyl terminal domain (CITED4). In 2010, it was reported that C/EBPB-CITED4 participated in exercise-induced cardiac growth. This chapter will introduce the C/EBPB-CITED4 signaling pathway and its effects on exercise-induced cardioprotection.

1 C/EBPB-CITED4 Signaling Pathway

1.1 Introduction of C/EBPB-CITED4 Signaling Pathway

C/EBPB are a member of a family C/EBPs. The basic leucine zipper (bZIP) domain is a highly conserved domain of this family, which mainly contributes to dimerization and DNA binding. In addition to C/EBPB, the family was also found to contain 5 other members (C/EBPA-C/EBPF). Among all of the members, C/EBPB is the most explored one since it forms homodimers as well as heterodimers with other C/EBP isoforms. These dimers can bind to a specific DNA sequence at the promoter region of the target genes [5–12].

At least three isoforms are known for C/EBPB: 38-KDa Full (Lap), 35-KDa Lap and 21-KDa Lip [12–17]. Different members of C/EBP family share the same C-terminal 55 ± 65 amino acid residues [13]. The bZIP domain of C/EBPB is located in the region where there is basic amino-acid-rich DNA-binding region followed by a dimerization motif termed the 'leucine zipper' [18–20]. The specific structure of the C/EBPB binds DNA and functions as an active regulator of many genes. C/EBPs can interacts with other bZIP or non-bZIP transcription factors to initiate protein proteins intractions [21–23]. The leucine zipper of the bZIP domain consists of a heptad repeat of alternating three- and four-residue sequence that forms an α-helices. Two such repeats are able to develop in a parallel manner to form a coiled-coil structure. In addition, an inverted Y-shaped structure is formed by the two α-helical basic regions dimerize. α-helical leucine zipper domain makes up the the vertical portion of the lower end of Y and the arm of the Y is formed by a single α helix, one from each monomer, which will bind to one-half of a palindromic recognition sequence [24, 25]. The basic region also hypothesis an α helical structure [26, 27]. LAP contains both the activation and the bZIP domains, whereas only the latter is present in LIP.

C/EBPB is located in chromosome 2 in mus musculus and chromosome 20 in Homo sapiens. After its first purified from rat liver in 1987 [14], C/EBPB was widely investigated. C/EBPB function as a transcription factor to regulate the expression of multiple genes. It plays an important role in various biological process, especially in cell proliferation and differentiation, cellular response to stimulus and the execution of specialized cellular function (Table 14.1). On the other hand,

Table 14.1 The function of C/EBPB

Biological processes	Description	Genes regulated/ signaling pathway	References	Year
Cell proliferation	Hepatocyte proliferation	TGF alpha- rat C/EBPB Asp-105 or mouse C/ EBPB Glu-217	[80–82]	1999, 2011
		PEPCK		
	Negative regulation of T cell proliferation	c-Myc	[83]	2006
	Cardiac growth	p38α-regulated genes	[33, 41, 61]	2006, 2010, 2016
		miR-17-3p-Par4- C/ EBPB		
	Keratinocyte survival and skin tumorigenesis	Ras signaling	[84]	2002
Cell differentiation and system development	Brown fat cell differentiation	PRDM16-C/EBPB transcriptional complex	[85–87]	2009, 2013, 2004
		FBXO9-C/EBPB		
		ETO/MTG8- C/EBPB		
	Differentiation and apoptosis of neuroblastoma cells	C/EBPB-p53/p21	[88]	2002
	Mammary gland development	PR	[89–91]	2000, 1999, 1998
	Osteoblast and adipocyte differentiation	Msx2- C/EBPB	[92–94]	2009, 2009, 2004
		mTOR-C/EBPB		
	Cartilage degradation in chondrocytes	MMP13	[95]	2012
Nucleic acid-templated transcription	Regulates transcription of FAK, happens in survival, growth, apoptosis, EMT and self-renew of cardiac fibroblast	Par4-C/EBPB-FAK	[67]	2015
	Regulates a function/process that happens in intestine regulates Apob		[96]	2000
	Negative regulation of hepatic stellate cells apoptosis	XEXD caspase inhibitory box(K-Phospho-T(217)VD)	[97]	2001
	Intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress	CHOP-C/EBPB pathway	[98]	1998
	Cellular response to amino acid stimulus	miR-155-C/EBPB	[99]	2010
Immune system process	Defense response to bacterium	–	[100]	2007
Response to stimulus	Response to lipopolysaccharide	Trib1-C/EBPB	[101]	2007
	Response to endoplasmic reticulum stress	GRP78 chaperone	[102]	2009
	Induces HIV-1 replication	APOBEC3G	[103]	2008

C/EBPB is also regulated through multiple factors, including cytokines, mitogens, hormones, nutrients and other stress factors. Such as, in astrocytes and renal mesangial cells C/EBPB mRNA expression can be induced by TNF-α, but in hepatocytes C/EBPB modulates nuclear-cytoplasmic translocation [28–31].

It has been studied for decades on the relationship between C/EBPB and heart. Back in 1999, scientists found that hypoxic stimulation could induce the generation of C/EBPB in cardiomyocytes from neonatal rat. It was also found that C/EBPB regulated various of genes that are related to ischemia, such as IL-8, angiotensinogen and intracellular adhesion molecule-1 (ICAM-1) [32]. Later, C/EBPB was proved as one of the major p38α MAPK-regulated transcription factors in proliferating cardiomyocytes [33]. In a recent study, C/EBPB was found to be closely related to cardiac inflammatory reaction during ischemia. An elevation of its expression is observed during cardiac embryonic development, after myocardial infarction (MI) and ischemic/reperfusion injury (IR) [34].

The other member in this pathway is CITED4, which was successfully cloned and added to the CITED family in 2002 [35]. It can bind p300/CBP via the CH1 domain and functions as a co-activator for transcription factor AP-2 [36]. In a previous study, CITED4 works as an inhibitor of hypoxia-inducible factor 1α(HIF-1α) which is related to the prognostic marker for tumor [37, 38]. Other studies claimed its role in the proliferation and adhesion of the colorectal cancer cell [39]. However, CITED4 is also closely related to the bioactivity of cardiomyocytes. After binding to CBP/p300, either in the cytoplasm or nucleus, it activates genes responsible for cardiomyocyte growth and proliferation. Forced expression of CITED4 also increased levels of cyclin D1, which is known to drive cardiomyocytes proliferation [40, 41].

1.2 C/EBPB and Exercise

The study of C/EBPB and exercises can be traced back to 1994. Studies showed that exercise was also associated with a large increase in transcription of C/EBPB in liver, which promotes the body recovery [42, 43]. Later on, the improvement in endoplasmic reticulum (ER) function is suggested to be a bridge between exercise and C/EBPB. Cardiac ER stress through accumulation of misfolded proteins plays a pivotal role in cardiovascular diseases [44–46]. Evidence supports that aerobic exercise training (AET) may reestablish cardiac ER homeostasis by attenuating oxidative stress, mitochondrial dysfunction and calcium imbalance. C/EBPB transgenic (TG) mice was used to investigate the role of C/EBPB in ER stress. C/EBPB TG mice exhibited increased insulin/IGF1 signaling apoptosis, decreased proliferation, and aggravated ER stress [34, 47–49]. These findings implying a possible negative relation exists between exercise and C/EBPB.

C/EBPB has been recognized as a transcription factor negatively related to skeletal health, adipogenesis and ER stress. Exercise has been proven to prevent marrow mesenchymal stem cell (MSC) adipogenesis, and thus reverse aging and osteoporosis

by limiting expression of the C/EBPB. In a tunicamycin induced ER stress model, C/EBPB revealed itself as a mechanically responsive transcription factor. The repression of C/EBPB increases the amount of fat in the bone marrow and improve skeletal resistance to ER stress [48].

Another important change after exercise is the change in energy metabolism.

Both C/EBPB and C/EBP mRNA are produced in response to elevated cAMP agents and glucocorticoids [16]. By contrast, in rat PC12 cells,the forskolin-induced activation of the cAMP protein kinase A signal-transduction pathway activates the transcription of the c-fos gene. This process generated by the translocation of C/EBPB from the cytoplasm into the nucleus [50]. Different from the above mechanism, in the a colorectal cancer cell line DKO-1 the antioxidant-induced nuclear translocation of C/EBPB is also mediated by a protein kinase A dependent phosphorylation, but of Ser299 [51]. C/EBPB binding to the PEPCK promoter at the cAMP response element (CRE) (−87/−74) and P3I (−248/−230) binding sites [52]. That result suggests the multiple roles of C/EBPB in mediating the metabolic changes after exercises.

2 C/EBPB-CITED4 Signaling Is a Novel Pathway in Cardioprotection

2.1 C/EBPB-CITED4 in Mediating Benefits of Exercise in Heart

Exercise training improves cardiac functions by inducing physiologic hypertrophy, and increased ability of resistance to injury. It has been widely accepted that exercise reduces initial ischemic injury [53], cardiac fibrosis [54], remodeling [55], ventricular dilatation [56], and cardiac dysfunction [4, 57]. However, the mechanism behind these benefits remains unclear.

In 2010, it was first discovered that C/EBPB-CITED4 mediates the cardiac beneficial effects during exercise. They found that the expression of C/EBPB relatively decreased in the early phase of endurance exercise. Knock-down of C/EBPB is genetically similar to many of the phenotypes seen in exercised hearts, like cardiac hypertrophy and cardiomyocyte proliferation [41]. In exercised hearts, C/EBPB negatively regulates CITED4, which is a transcription factor promoting cardiomyocyte proliferation. Besides that, C/EBPB regulated the expression of the gene set characteristic of physiological hypertrophy by sequestering serum response factor. The results demonstrate that the reduction of cardiac C/EBPB plays a central role in exercise-induced cardiac growth, and C/EBPB-CITED4 pathway is an important signal in physiologic hypertrophy and proliferation.

The effects of CITED4 in adult heart was not explored until 2016. Cardiac specific CITED4 transgenic mice were used to determine the role of CITED4 in physiologic hypertrophy, and it was found that these mice had an increased heart weight

with normal systolic function [58]. This share the similar phenotype of heart underwent endurance exercise. Cardiomyocyte size in iCITED4 transgenic heart was increased but EdU incorporation of PCM1-positive cardiomyocytes at baseline remained unchanged. The histologic findings supported that CITED4 was responsible for the physiological hypertrophic changes in heart after endurance exercise training. Moreover, CITED4-overexpression could improve cardiac function after ischemia-reperfusion injury by activation the mTORC1 pathway [58].

2.2 *C/EBPB-CITED4 Is Important to Cardiac Growth in Pregnancy*

Besides exercise induced physiological cardiac hypertrophy model, pregnancy induced physiological cardiac hypertrophy is another model [59, 60]. C/EBPB has also been found to be necessary for hypertrophy while other C/EBP subtypes (A and D) do not have this effect [61]. Interestingly, the IL-6 expression in the heart of pregnant mice was blocked in C/EBPB+/− animals. Stimulated by LPS, M2-macrophage gene expression was inhibited, indicating ogestation. In addition, after ischemia, C/EBPB appears as a transcription factor required for cardiac hypertrophy in response to reperfusion in the heart. This can be explained by the fact that pregnancy reduced fibrosis in C/EBPB+/−mice [62, 63]. From this we can infer that C/EBPB is mediating cardiac benefits of pregnancy induced physiological hypertrophy as well.

2.3 *A Regulatory Network Based on C/EBPB-CITED4 Signaling Pathway*

C/EBPB have the ability to induce physiological cardiac growth at least partly via CITED4. Exercise can induce a transcriptional network distinct from that seen under pathological stimuli, even at an early stage when the hearts were structurally and functionally indistinguishable. In addition, physiological growth was associated with transcriptional components linked to cell-cycle progression. Exercised hearts showed an increase in proliferation markers. Interestingly, various factors have been reported to be involved in cardiac response to exercise by affecting C/EBPB [64, 65]. Of note, miR-222 can act as upstream modulator of CITED4, but the interaction of between the two remains discussible. Overall, the complex regulatory network of C/EBPB and CITED4 has not been fully revealed.

2.3.1 MicroRNAs

MicroRNA (miRNA, miR) is an important posttranscriptional regulator, participating in various physiologic activities, especially in cardiac physiologies [66].

MiR-222 is an essential miRNA for exercise-induced cardiac growth. It also works by activating CITED4 [64]. Researchers firstly found that cardiac miR-222 increased in both voluntary wheel running and a ramp swimming exercise mice model. The gain- and loss-of-function experiment in vitro shows that miR-222 contributes to the growth, proliferation, and survival of cardiomyocytes by targeting p27, HIPK1 and HMBOX1. Interestingly, the research indicated that miR-222 mediates above functions through different target genes. The interaction between miR-222 and C/EBPB-CITED4 pathway was further discussed, they knock down p27 or Hmbox1, two of the main target gene of miR-222, the proliferation of cardiomyocyte was promoted with the an increase in CITED4 independent of C/EBPB expression. In contrast, knockdown of p27 and HIPK1 simultaneously did not significantly alter the expression of CITED4 and actually increased C/EBPB expression. These data indicate a complex regulatory network between these factors.

Another miRNA, miR-17-3p is reported to be an inhibitor of mouse cardiac fibroblast senescence [67]. miR-17-3p overexpression could inhibit cardiac senescence and apoptosis in a mouse cardiac fibroblast (MCF) cells and in transgenic mice. In particular, miR-17-3p can repress the expression of Par4 to enhance epithelial-to mesenchymal transition (EMT) and self-renewal of MCFs. As a downstream of Par4, the transcription of C/EBPB and FAK were also enhanced by miR-17-3p indirectly during this process. A very recent study also found that miR-17-3p was necessary for exercise-induced cardiac growth and played an important role in protecting against myocardial ischemia-reperfusion injury. But if miR-17-3p could regulate C/EBPB and CITED4 in cardiomyocytes is unclear [68]. The relationship between miR-17-3p and C/EBPB in the exercises heart still deserves further exploration.

2.3.2 Other Molecules Related to the C/EBPB Signaling in Heart

The function of C/EBPB in the pathological model is also investigated in heart. C/EBPB knockdown inhibited phenylephrine (PE)-induced cardiac hypertrophy, and diminished the nuclear trans-location and DNA binding activity of p65- NF-kB. Thus, C/EBPB knockdown could protect cardiac pathological hypertrophy through inhibiting NF-kB dependent transcriptional activity [65]. These findings shed new light on the understanding of C/EBPB-related cardiomyopathy, and suggest the potential therapeutic effect of C/EBPB inhibitors in cardiac hypertrophy [65, 69–71].

Alpha-lipoic acid (ALA) is a naturally occurring compound, exerting powerful protective effects in numerous cardiovascular disease [72]. A direct anti-hypertrophic effect of ALA was reported on cardiomyocyte [72]. In addition, hypertrophy induced by PE could also be attenuated by ALA, and hypertrophy biomarkers such as ANP and BNP were also reduced. When these cardiomyocytes were co-transfected with

C/EBPB, ALA failed to inhibit hypertrophic responses. However, pretreated with ALA could in turn markedly suppress the upregulated C/EBPB, thus counteracting its hypertrophic effect. Taken together, ALA has a robust anti-hypertrophic and anti-remodeling effect, which is mediated by inhibition of C/EBPB activation [73]. This result also provide evidence for the important role of C/EBPB in the cardioprotection. Under the regulation of various upstream factors, C/EBPB eventually overexpressed and mediate the benefit of exercises in heart. Nevertheless, the role of CITED4 in this process is not clear.

3 Conclusion and Prospect

Cardiac remodeling induced by exercise is mainly related to cardiomyocytes hypertrophy and renewal [74–76]. Under certain circumstances, the heart shows the adaptive response by increasing cardiomyocytes contractility, cell survival, metabolic and mitochondrial adaptations, electrical remodeling, arcomeric remodeling and angiogenesis. A sustained effort over the past three decades to uncover the cellular and molecular basis of the cardiac protection effect of exercise now yielding imminent success in this field. The roles of cardiac transcription factors in cardiac pathological hypertrophy have been identified, including GATA Transcription Factors [69, 77], MEF2 transcription factors [78, 79], and cardiac homeobox transcription factor [74]. As a transcriptional factor which has the potential in mediating the protect effect of exercises in heart, the role of C/EBPB is at largely unexplored.

It should be noted that now it is recognized that C/EBPB-CITED4 signaling pathway is the essential part of the physiological cardiac hypertrophy. This is fundamental changes in heart histology for cardiac protection of both exercises and pregnancy. From the previous study, we can conclude that as a transcriptional activator, C/EBPB has the potential in regulating a lot of gene expression. The effects of C/EBPB are partly via the cited dependent pathway, and CITED4 independent pathway also have its own value.

Several studies are highly needed. Firstly, the upstream of C/EBPB in the heart needs to be determined. Secondly, the cross talk between C/EBPB and many other signaling pathways, including the other typical signaling pathway during exercise, such as IGF1-PI3K, NO signaling pathway, is unclear.

In conclusion, C/EBPB and CITED4 are critical regulators of cardiac physiological hypertrophy. Inhibition of C/EBPB or activation of CITED4 represents a novel way to treat cardiac remodeling and heart failure.

Competing Financial Interests The authors declare no competing financial interests.

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Chapter 15
MicroRNAs Mediate Beneficial Effects of Exercise in Heart

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Abstract MicroRNAs (miRNAs, miRs), a group of small non-coding RNAs, repress gene expressions at posttranscriptional level in most cases and are involved in cardiovascular physiology and disease pathogenesis. Increasing evidence has proved that miRNAs are potential regulators of exercise induced cardiac growth and mediate the benefits of exercise in a variety of cardiovascular diseases. In this chapter, we will review the regulatory effects of miRNAs in cardiac adaptations to exercise, and summarize their cardioprotective effects against myocardial infarction, ischemia/reperfusion injury, heart failure, diabetic cardiomyopathy, atherosclerosis, hypertension, and pulmonary hypertension. Also, we will introduce circulating miRNAs in response to acute and chronic exercise. Therefore, miRNAs may serve as novel therapeutic targets and potential biomarkers for cardiovascular diseases.

Keywords MicroRNA • Exercise • Cardiovascular diseases

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1 Introduction

Cardiovascular diseases (CVDs) are major causes of morbidity and mortality worldwide [1]. Currently, despite continuous advances achieved in clinical treatments including medical and surgical therapies, CVDs are still considered to be major diseases and exert a considerable emotional and economic burden [2]. In light of these, development of innovative therapeutic strategies for CVDs are urgently needed.

Physical exercise, as well as pregnancy and postnatal cardiac growth, are major stimuli for physiological cardiac hypertrophy [3]. For many years, cardiologists advocated prolonged rest for patients with CVDs especially ischemic heart diseases [4]. However, increasing number of studies have validated the multiple benefits of physical exercise in comparison to the detrimental effects of a sedentary lifestyle, making physical exercise a therapeutic modality for patients with a variety of chronic diseases, such as CVDs, type II diabetes, fatty liver, stroke, disseminated sclerosis, and malignant tumor [5–11]. Among them, further studies have demonstrated that individuals with proper level of physical exercise have lower prevalence and death rate for CVDs [12]. Thus, physical exercise has been established not only as a mean to maintain a healthy lifestyle but also as a safe and important nonpharmacological way for prevention and treatment of CVDs.

Non-coding RNAs (ncRNAs) are a diverse group of functional RNA molecules without protein-coding functions, which may range from short microRNAs (~22 nucleotides) to long non-coding RNAs (>200 nucleotides) [13, 14]. MicroRNAs (miRNAs, miRs) repress gene expressions at posttranscriptional level in most cases and are involved in various cellular processes, including differentiation, proliferation, apoptosis, migration, angiogenesis, and so on [15]. Importantly, mounting data have suggested that ncRNAs, especially miRNAs, could lead to a profound regulation of target genes and related signaling pathways, thus engaging in a variety of beneficial effects of exercise in the heart [16, 17]. This may raise a hope that miRNAs may serve as potential therapeutic targets mediating the benefits of physical exercise to combat CVDs.

In this chapter, we will provide an overview of the protective effects of physical exercise on diverse CVDs and the involvement of miRNAs in this process.

2 Cardiac Adaptations to Physical Exercise

2.1 Cardiac Growth: Cardiac Hypertrophy and Cardiomyocyte Renewal

Cardiac hypertrophy is an adaptation to increased cardiac workload including a variety of mechanical, hemodynamic, and hormonal factors [18]. There are two different forms of ventricular hypertrophy, namely physiological hypertrophy and pathological hypertrophy [19]. Both hypertrophic processes involve increased

cardiomyocyte size, enhanced protein synthesis, and recombination of sarcomere structure. However, cardiac physiological hypertrophy differs from pathological hypertrophy in its stimuli and its structural and functional adaptations [4, 20–22]. As for stimuli, physiological hypertrophy occurs in healthy individuals following exercise training, pregnancy, or postnatal growth [23, 24], while pathological hypertrophy is associated with hypertension, or loss of myocytes due to ischemic or hypoxic myocardium damages [21]. As for structural and functional adaptations, physiological hypertrophy caused by endurance exercise training mainly exhibits ventricular hypertrophy with addition of sarcomeres and increase of cell length and cardiac mass, leading to preserved even enhanced left ventricular function, reduced collagen content, and improved myocardial antioxidant capacity and mitochondrial function [22, 25]. However, besides addition of sarcomeres, pathological hypertrophy is also characterized by increased cell thickness, enhanced apoptosis, and impaired cardiomyocyte metabolism switching from fatty acid to glucose metabolism, which could ultimately lead to increased cardiac fibrosis and stiffness and progressive reduction in cardiac output [26–28].

Over the past decades, the adult mammalian heart has been considered as a post-mitotic organ without any regenerative capacity [29]. However, more recent evidence has contradicted the long established belief, indicating that the adult mammalian heart sustains certain endogenous growth and regenerative capacity under some physiological or pathological conditions [30]. Actually, nearly half of cardiomyocytes are replaced during a whole human lifespan [30]. In a normal mouse heart, the turnover rate of cardiomyocytes is nearly 1.3–4.0% per year, while after myocardial injury, the rate of cardiomyocyte renewal is significantly increased, especially in the infarct border zone [31]. Importantly, physical exercise is shown as a novel strategy to endogenously enhance the limited capacity of cardiomyocytes for proliferation [32]. The potential sources of newly formed cardiomyocytes could be originated from division of pre-existing cardiomyocytes or differentiation of cardiac stem/progenitor cells [33, 34].

2.2 Angiogenesis

In cardiac physiological hypertrophy, the coordinated growth of myocardium and vasculature is an important adaptation of heart to deliver enough oxygen to the myocardium [35]. It was reported that endogenous cardiac stem cells (eCSCs) can be activated upon exercise [34]. Interestingly, these c-kit positive eCSCs were also committed to Nkx2.5 positive or Ets-1 positive cell lineages, indicating their potential to differentiate into both cardiomyocytes and vascular cells [34]. In addition, endothelial progenitor cells (EPCs), a type of circulating monocytes derived from bone marrow, can also be activated in response to exercise [36]. Acute exercise leads to a rapid increase in circulating EPCs that can maintain for up to 2–3 days after exercise termination. Furthermore, systematic and chronic exercise is able to trigger the mobilization of EPCs into the circulation from the bone marrow in both

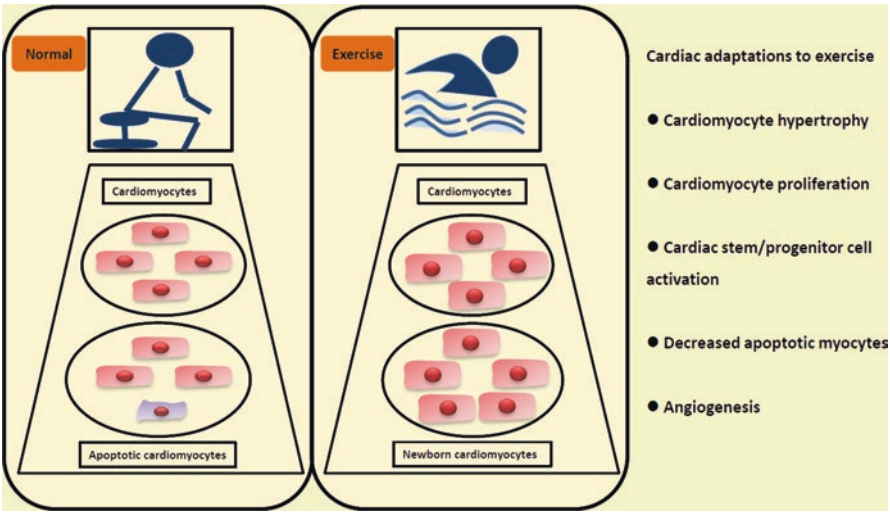

Fig. 15.1 Cardiac adaptations in response to physical exercise

healthy or diseased individuals [37]. Given the capacity of EPCs to proliferate, migrate, and differentiate into mature endothelial cells which contributes to neovascularization, exercise via promoting angiogenesis, may act as an important physical strategy or compensatory mechanism for cardiac regeneration and repair.

Taken together, the physiological adaptation of adult heart to exercise has three main components: (1) physiological hypertrophy of cardiomyocytes; (2) renewal of cardiomyocytes originated from pre-existing cardiomyocytes or cardiac stem/progenitor cells; (3) the accumulation of new microvasculature (Fig. 15.1). These cardiac physiological adaptations to physical exercise can lead to increased cardiac mass and even enhanced cardiac function.

3 miRNAs Responsible for Cardiac Adaptations to Exercise

Currently, miRNAs are emerging as pivotal modulators of cardiovascular development and disease [38, 39]. miRNAs have also been reported to participate in the beneficial adaptations promoted by exercise including physiological cardiac hypertrophy (Table 15.1).

3.1 Cardiac Growth

miR-1 and miR-133 were firstly reported to be decreased in both physiological hypertrophy induced by treadmill exercise and pathological hypertrophy induced by pressure overload [40]. After that, the other study also demonstrated that miR-1 and

Table 15.1 miRNAs responsible for cardiac adaptations of exercise

Type of exercise	Cardiac adaptation	miRNA	Target genes	References
Running (interval exercise)	Hypertrophy	↓miR-1, ↓miR-133	RhoA, Cdc42, Nelfa	[40]
Swimming (continuous exercise)	Hypertrophy	↓miR-208a	Purβ	[43]
Swimming (continuous exercise)	Hypertrophy	↑miR-27a/b	ACE	[44]
		↓miR-143	ACE2	
Swimming (continuous exercise)	Hypertrophy	↑miR-21, miR-144	PTEN	[46]
		↑miR-145	TSC2	
		↓miR-124	PI3Kα	
Running/swimming (continuous exercise)	Hypertrophy/Proliferation	↑miR-222	p27, HIPK1, HMBOX1	[47]
Running/swimming (continuous exercise)	Hypertrophy/Proliferation	↑miR-17-3p	TIMP3	[48]
Swimming (continuous exercise)	Anti-fibrosis	↑miR-29c	Collagen I, Collagen III	[41]
Swimming (continuous exercise)	Angiogenesis	↑miR-126	Spread1, PI3KR2	[38]

miR-133a/b were down-regulated in physiological cardiac hypertrophy induced by two different swimming protocols, indicating that these miRNAs could be regulated by exercise regardless of exercise mode or volume (moderate and high) [41].

Unlike in pathological hypertrophy [42], the expressions of miR-208a and miR-208b were reduced in exercise group compared with sedentary group, parallel to an increase of target gene transcriptional activator protein Pur-beta (Purβ) [17, 43]. Interestingly, overexpression of Purβ inhibited β-MHC expression accompanied by increased α-MHC expression and improved ventricular compliance, suggesting that down-regulation of miR-208 may mediate the beneficial effect of exercise against CVDs [43].

It is well known that angiotensin (Ang) II is an inducer for cardiac pathological hypertrophy, while exercise-induced physiological hypertrophy is associated with increased Ang-converting enzyme 2 (ACE2) activity, which might protect against pathological hypertrophy via reducing Ang II [44]. miR-27a and miR-27b have been reported to be increased in exercise-induced physiological hypertrophy in rats and they could target ACE, while decrease of miR-143 could lead to increased ACE2 activity and reduced Ang II level [44, 45].

The phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling is critically involved in the regulation of cellular proliferation and survival, and plays a positive role in exercise-induced cardiac physiological hypertrophy [46]. Exercise could elevate cardiac miR-21 and miR-144 expressions, which were both predicted by bioinformatic analysis to target phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/Akt/mTOR pathway. Besides that, miR-145 was also found to be increased after exercise training, accompanied by a decrease in its target gene tuberous sclerosis

complex 2 (TSC2, another negative regulator of the PI3K/Akt/mTOR pathway). Moreover, exercise training decreased cardiac miR-124 expression with an increase in its target gene PI3K (p110α) [46].

Cardiomyocyte hypertrophy, as well as proliferation, are two important cellular changes during physiological cardiac growth. Recently, miR-222 and miR-17-3p have been reported to be increased in exercised heart and are necessary for exercise-induced cardiac growth [47, 48]. miR-222 can directly target P27 and HIPK1 in the regulation of cardiomyocyte proliferation, while target HMBOX1 in the regulation of cardiomyocyte hypertrophy [47]. Moreover, miR-17-3p enhances cardiomyocyte proliferation via targeting TIMP3, and induces cardiomyocyte hypertrophy by inhibition of PTEN and subsequent activation Akt [48]. However, overexpression of miR-222 or miR-17-3p alone was not sufficient to recapitulate the phenotypes of physiological growth as seen in exercised heart, suggesting that these miRNAs might work together to promote exercise-induced physiological cardiac growth in vivo [47, 48].

3.2 Anti-fibrosis

miR-29c was significantly increased in cardiac physiological hypertrophy induced by swimming exercise, and its target genes including collagen IAI and collagen IIIAI were both decreased [41]. Exercise-associated increase in miR-29c was correlated with reduced collagen concentration in the heart and improved left ventricular compliance, implying an anti-fibrosis effect of miR-29c, which might also exert protective effects against pathological cardiac remodeling [49].

3.3 Angiogenesis

Vascular endothelial growth factor (VEGF) has been reviewed as an important mediator of angiogenic responses upon different stimuli, including exercise [50]. Exercise training could promote vessel growth by increasing the expression level of miR-126 and repressing its target genes including sprouty-related protein 1 (Spread-1) and phosphoinositol-3 kinase regulatory subunit 2 (PI3KR2), which are two negative regulators of VEGF by inhibiting the PI3K/Akt/endothelial nitric oxide synthase (eNOS) pathway [38, 39].

Taken together, these data indicate that exercise can promote physiological cardiac hypertrophy through regulation of miRNAs and their specific target genes (Table 15.1). These miRNA-mRNA interactions may contribute to cardiac growth, anti-fibrosis, and angiogenesis processes in the heart upon exercise, and also probably mediate the protective effect of exercise against CVDs.

4 miRNAs Mediate Protective Effects of Exercise in CVDs

Exercise-induced cardiac protection has been appreciated for many decades, and several canonical molecular mechanisms have been proposed to contribute to the benefits of exercise. As novel mechanism, incorporating miRNAs within cardiac gene regulatory networks may provide a new opportunity for developing therapeutic interventions for CVDs.

4.1 Exercise Protects Against Myocardial Infarction

Myocardial infarction (MI) occurs when blood flow stops to a part of the myocardium causing damage to the heart muscle [51]. MI is accompanied by cardiomyocyte apoptosis, and necrosis, and hypertrophy, increased collagen deposition, and new vascularization, which results in pathological cardiac remodeling and reduced ventricular compliance [52]. As we described previously, exercise training could induce miR-29a and miR-29c in the heart, leading to reduced collagen concentration and improved ventricular compliance in healthy rats [41]. Interestingly, exercise training could also restore cardiac miR-29a and miR-29c expression levels and reduce collagen type I and III expression levels in the border and remote areas of MI [53]. This suggests an anti-fibrosis effect of exercise in rats with MI through upregulating miR-29a and miR-29c, which might serve as potential therapeutic strategy to reduce infarct size and improve cardiac function in MI patients [53].

On the other hand, impairment of cardiomyocyte contractility and calcium handling are hallmarks of left ventricular contractile dysfunction in MI [54]. Aerobic intensity-controlled interval training attenuated myocardial hypertrophy and increased myocyte contractile function in post-MI rats, accompanied with upregulated sarcoplasmic reticulum Ca2 + -ATPase 2a (Serca-2a) and sacolemmal sodium/calcium exchanger (NCX) protein levels, and enhanced intracellular Ca2+ handling and Ca2+ sensitivity in cardiomyocytes from rats with MI [55]. MI could also decrease miR-1 and increase miR-214, while exercise after MI partially restored miR-1 and miR-214 by targeting NCX and Serca-2a, respectively [56]. These molecular adaptations were associated with improved left ventricular compliance in MI hearts, and thus exercise was supposed to have a positive impact on Ca2+ handling, via regulating miR-1 and miR-214, in hearts post-MI [56].

Additionally, miR-26a was shown to be increased in mouse acute MI and human acute coronary syndromes [57]. Overexpression of miR-26a, via inhibiting its target gene SMAD1, could lead to impaired tube formation of endothelial cells in vitro and reduced angiogenesis upon exercise in vivo [57]. Interestingly, inhibition of miR-26a was associated with robust angiogenesis, reduced infarct size, and improved cardiac function even within 2 days after MI [57]. This suggests miR-26a as an important miRNA regulating angiogenetic response in ischemic cardiac diseases.

4.2 Exercise Protects Against Cardiac Ischemia/Reperfusion Injury

Cardiac ischemia/reperfusion (I/R) injury refers to heart damage caused when blood supply returns to the heart after a period of ischemia or lack of oxygen, which then induces a series of pathological changes including oxidative stress, inflammatory responses, Ca2+ overload, mitochondrial dysfunction, and myocardial apoptosis [58]. Burgeoning evidence indicates that physical exercise can protect against I/R injury in both clinical patients and experimental animal models by upregulating anti-oxidative capacity, promoting angiogenesis, and decreasing cardiomyocyte apoptosis [59–61]. Recently, miRNAs have been reported to underline these mechanisms mediating the protective effects of exercise against I/R injury.

miR-222 is a highly conserved member of a miRNA cluster with miR-221, which is encoded on the X chromosome [62, 63]. miR-222 has been found to be increased in the plasma of athletes after both acute and chronic exercise, suggesting a potential relevance of miR-222 with exercise [64]. Interestingly, circulating miR-222 could also be elevated after acute cardiopulmonary exercise in heart failure patients, indicating a potential role of miR-222 in mediating the beneficial effect of exercise in heart failure patients [47]. More importantly, miR-222 was proved to be necessary for exercise-induced physiological growth by promoting both hypertrophy and proliferation of cardiomyocytes through targeting P27, HIPK1, and HMBOX1 [47]. Although overexpression of miR-222 was not sufficient to recapitulate the exercise phenotype at baseline, it did protect against adverse ventricular remodeling and cardiac dysfunction after I/R injury [47]. These effects were also associated with inhibition of cardiomyocyte apoptosis and a dramatic reduction of cardiac fibrosis [47].

As overexpression of miR-222 alone was not sufficient to recapitulate the phenotypes of physiological growth observed in exercised heart, we also speculated that other molecular mechanisms (including miRNAs) must be involved in this process. Recently, miR-17-3p, a passenger miRNA that belongs to the miR-17-92 cluster, was also proved to be necessary for exercise-induced cardiac growth and have protective effects against cardiac remodeling after I/R injury, which was at least in part due to enhanced proliferation and reduced apoptosis of cardiomyocytes [48].

4.3 Exercise Protects Against Heart Failure

Heart failure (HF) often refers to congestive heart failure and occurs when the heart is unable to pump enough blood to meet the body's needs [65]. Accumulating studies indicate that exercise training has protective effect on the myocardium in patients with HF and in animal models of pathological cardiac hypertrophy and HF, which could be associated with increased exercise tolerance, improved cardiac structure and function, and reduced HF-related biomarkers during cardiac remodeling [66–70].

Currently, exercise training has been formally recommended by major guidelines as a safe and important strategy for patients with HF [71, 72]. However, the molecular mechanisms by which it exerts the therapeutic value for HF are far from understood.

Recently, Souza RW et al. conducted a miRNA expression profile in ascending aortic stenosis-induced HF rats randomized to either 10 weeks of exercise training or sedentary group [66]. Therapeutic effects of exercise in reducing cardiac remodeling and maintaining systolic and diastolic function were associated with differentially regulated miRNAs between exercise and sedentary group, including miR-208b-3p, miR-21-5p, miR-132-3p, and miR-212-3p [66]. Interestingly, some of these miRNAs were reported to regulate I/R injury or cardioprotection by ischemic pre- and post-conditioning [73–77]. Further gene-term enrichment analysis showed that these differentially regulated miRNAs between exercised or sedentary HF rats could target genes involved in programmed cell death, TGF-β signaling, cellular metabolic process, cytokine signaling, and cell morphogenesis. Among these five biological modules, programmed cell death module compromise the most enriched miRNA targets, indicating that exercise may attenuate cardiac abnormalities during HF by regulating miRNAs through apoptosis-related pathways [66].

4.4 Exercise Protects Against Diabetic Cardiomyopathy

Diabetes mellitus (DM) is a group of metabolic diseases in which there are high blood sugar levels over a long period [78]. Several recent epidemiological studies have confirmed that DM was an independent predictor for heart disease and would influence 400 million people worldwide by 2030 with prevalent cardiovascular deaths [79–81]. Exercise has been described as a polypill that prevents myocardial apoptosis and fibrosis, ameliorates mitochondrial biogenesis, and preserves cardiac function in diabetic cardiomyopathy in mice [82]. Furthermore, exercise can also mitigate cardiac dysfunction in diabetic patients though the molecular mechanisms still remain uncertain [83].

Exosomes are small membrane vesicles (30–100 nm) that contain various biological contents like DNA, RNA, protein, as well as miRNA, thus participating in cell-to-cell communications [84]. Extracellular vesicles derived from stem cells or even from plasma of healthy individuals have been documented to diminish cardiomyocyte apoptosis and improve cardiac function after ischemic cardiac injury, suggesting exosomes as critical agents for cardiac repair [85, 86]. Exercise training could trigger the release of exosomes that contain miRNAs (miR-455, miR-29b, miR-323-5p, and miR-466) from diabetic hearts compared to sedentary diabetes group. Interestingly, these miRNAs were proved to bind to the 3′ region of matrix metallopeptidase 9 (MMP9) and thus silence MMP9, a gene regulating extracellular matrix remodeling [87]. Thus, a close relationship has been suggested between exercise-derived exosomes, exosomal miRNAs, and the benefit of exercise for the heart, which could delineate novel strategy to cope up with diabetic cardiomyopathy.

4.5 Exercise Protects Against Atherosclerosis

Atherosclerosis (AS), a disease associated with chronic inflammation, is characterized by thickened artery wall linked to invasion and accumulation of foam cells, proliferation of intimal smooth muscle cells, and finally formation of atheromatous (fibrofatty) plaque in the arteries [88, 89]. Actually, physical exercise is also recommended as an effective way to diminish vascular injuries in patients with AS, probably by reducing triglyceride and apolipoprotein B, enhancing tissue plasminogen activator activity, and decreasing coronary artery calcium [90, 91]. Exercise was able to reduce foam cell accumulation and plaque formation, accompanied with an increase in vascular miR-146a and miR-126 expression levels, and a decrease in vascular miR-155 expression level in apolipoprotein E-null mice fed with high-fat diet [92]. Importantly, miR-146a was further demonstrated to directly target tumor necrosis factor receptor 6 (TRAF6), a gene involved in the Toll-like receptor 4 (TLR4) signaling pathway, suggesting that exercise-induced miR-146a may protect against AS by repressing vascular inflammatory injury [92].

4.6 Exercise Protects Against Hypertension

Hypertension is a long term medical condition in which the blood pressure in the arteries is persistently elevated [93]. Long term high blood pressure represents a major risk factor for CVDs [93]. Exercise training is established as a nonpharmacological tool for treatment of hypertension by improving endothelial function, attenuating microvascular rarefaction, and reducing blood pressure [94, 95]. Exercise is also effective in reducing other CVD risk factors in patients with hypertension as evidenced by improved plasma lipoprotein-lipid profiles and insulin sensitivity [96].

For further detecting the underlying mechanisms, some studies focused on the change of miRNAs in response to exercise in hypertension. Exercise training has been found to be able to significantly reduce blood pressure and heart rate in spontaneously hypertensive rats (SHR) compared to sedentary SHR group, by regulating several angiogenesis-related miRNAs [97]. Previous studies indicated that miR-16 via targeting VEGF and Bcl-2, miR-21 via targeting Bcl-2, and miR-126 via targeting sprouty-related protein 1 (Spread-1) and phosphoinositol-3 kinase regulatory subunit 2 (PI3KR2), lead to the dysregulation of angiogenesis and apoptosis processes [98–101]. Interestingly, exercise could restore the increased miR-16 and miR-21, and the decreased miR-126 expression levels in the soleus of hypertensive rats [97]. Exercise could also activate the VEGF and anti-apoptotic signaling pathways and improve endothelial nitric oxide synthase (eNOS) level as well [97]. These data provide evidence that exercise can balance angiogenic and apoptotic pathways by regulating miRNAs, and thus prevent microvascular abnormalities in hypertension [97].

4.7 Exercise Protects Against Pulmonary Hypertension

Pulmonary hypertension (PH) refers to an increase of blood pressure in the pulmonary arterial system. Pulmonary arterial hypertension (PAH) is the most common form characterized by sustained vasoconstriction, vascular remodeling of small pulmonary arteries, in situ thrombosis, and chronic inflammation, that leads to increased mean pulmonary arterial pressure and ultimately right heart failure and death [102]. Despite significant progress in treatment, the three-year survival of patients with PAH is a little bit higher than 50% and the quality of life remains severely affected [103]. More recently, a body of clinical evidence has shown the safety and efficacy of exercise training in PAH [104, 105]. Exercise training was demonstrated to be effective to enhance exercise tolerance, improve quality of life, and possibly increase survival rate in patients with PAH associated with connective tissue diseases [106]. Exercise training could also significantly lower right ventricular end diastolic pressure, reduce pulmonary artery thickness, and decrease right ventricular interstitial volume in monocrotaline-induced PAH [107]. Despite the certain beneficial effect of exercise on PAH, the mechanisms involved especially the role of miRNAs need to be further explored.

5 Circulating miRNAs in Response to Exercise

Circulating miRNAs (c-miRNAs) are the most investigated ncRNAs detected in the serum or plasma of humans and animals. c-miRNAs are usually protected from degradation as they can be packaged into membrane vesicles such as exosomes or microvesicles [108]. Additionally, c-miRNAs can be packaged into lipoproteins or Ago proteins as part of RNA-induced silencing complexes [109, 110]. As c-miRNAs can be released at rest or upon tissue injury or physiological stress such as exercise training, c-miRNAs may serve as unique biomarkers of disease states and exercise physiology [111–113].

The dose-response relationship between leisure-time physical activity and mortality was investigated by a pooled analysis, and it was indicated that moderate- or even vigorous-intensity physical exercise was associated with longevity benefit [114]. Noteworthy, no excess mortality risk was found even with ten times the recommended minimum level of leisure-time physical exercise [114]. Thus, leisure-time physical exercise should be highly recommended to inactive individuals [114]. Increasing number of studies reported the alteration of c-miRNAs implicated in muscle adaptations, angiogenesis, and inflammation during physical exercise. However, little is known about the effects of different type, intensity, and duration of exercise on c-miRNAs. In this section, we will summarize the potential changes of major c-miRNAs in response to different modes of exercise.

5.1 Circulating miRNAs in Acute Exercise

miR-1, miR-133, miR-206, miR-208b, and miR-499, also called muscle-enriched miRNAs (myomiRs), are highly abundant in cardiac and/or skeletal muscles while their expression levels in circulation are very low in healthy individuals [115]. An acute bout of endurance exercise (marathon) could induce the rapid increase of circulating miR-1, miR-133a, miR-206, miR-208b, miR-499, and miR-206, supporting the notion of distinct c-miRNA changes would in response to exercise [116]. Twenty-four hours after the marathon run, miR-208b and miR-499 returned to baseline levels, while other c-miRNAs still enhanced [116]. Moreover, miR-1, miR-133a, and miR-206 expression levels were positively correlated with the maximum oxygen uptake (VO2max), an indicator of exercise capacity, while no correlations were found between c-miRNAs and cardiac damage biomarkers such as troponin T and troponin I, indicating that the release of myomiRs into circulation might be used as unique biomarkers for exercise physiology rather than consequences of cell death [116]. However, another study reported that circulating miR-1 and miR-133a were increased immediately after marathon, but declined very close to baseline levels 24 hours after race completion [113]. Interestingly, circulating miR-133a has also been reported to be unchanged after an acute exhaustive exercise test, suggesting that the regulation of c-miRNAs might be closely related to exercise type, intensity, and duration [64].

miR-126 is enriched in vascular endothelium and miR-146a is an important regulator of inflammation [117, 118]. Circulating miR-146a and miR-126 were both increased immediately after a marathon run, and rapidly returned to baseline levels 24 hours later [113]. However, in another study, circulating miR-146 was down-regulated immediately after an acute exercise bout in young healthy men [119]. In addition, circulating miR-146a level has also been reported to be unchanged at 0 h, 1 h, and 24 h after an acute resistance exercise, while it began to decrease at 3 days post exercise in healthy young males [120]. These different regulatory patterns of c-miRNAs indicate that participants, as well as exercise type, intensity, and duration may affect changes of c-miRNAs in response to exercise.

Some other miRNAs have also been found to be modulated by exercise. miR-106a, miR-221, miR-30b, miR-151-5p, let-7i, miR-146a, miR-652, and miR-151-3p were robustly down-regulated immediately after an acute exercise bout. miR-338-3p, miR-330-3p, miR-223, miR-139-5p, and miR-143 were up-regulated at 1 hour after exercise and miR-1 was elevated at 3 h after exercise [119]. Additionally, a rapid decrease of muscle-enriched miR-486 in circulation after an acute exercise was found [121], indicating that exercise may reduce the release of myomiRs into circulation, or perhaps accelerate the uptake of specific c-miRNAs from circulation into certain recipient tissues and cells, though the mechanisms remain largely unknown.

Table 15.2 Circulating miRNAs in response to exercise

Types of exercise	Categories	Changed c-miRNA	References
Acute exercise			
Marathon running	Athlete	↑miR-1/133a/206/208b/499	[113, 116]
Marathon running	Athlete	↑miR-146a/126	[113]
Cycle ergometer exercise	Normal	↓miR-146a	[119, 120]
Cycle ergometer exercise	Normal	↓miR-106a/221/30b/151/652/let-7i	[120]
		↑miR-338-3p/330-3p/223/139-5p/143/1	
Chronic exercise			
Rowing exercise training	Athlete	↑miR-20a	[64]
Cycle ergometer exercise	Normal	↓miR-342-3p/766/25/148a/185/21/let-7d	[119]
		↑miR-103/107	

5.2 Circulating miRNAs in Chronic Exercise

Little is known about the regulation and function of c-miRNAs in chronic exercise. After 12 weeks of chronic endurance training, miR-342-3p, miR-766, let-7d, miR-25, miR-148a, miR-185, and miR-21 were decreased while miR-103 and miR-107 were increased in plasma [119]. In addition, circulating miR-20a was increased after a 90 days period of rowing training, but not affected by acute exercise in healthy competitive athletes [64]. Noteworthy, the change in circulating miR-20a quantitatively correlated with the change in VO2max, indicating a potential role of miR-20a as a biomarker for chronic exercise fitness [64]. The altered circulating miRNAs in response to exercise were listed in Table 15.2.

6 Conclusions

In this chapter, we summarize the current knowledge about miRNAs responsible for cardiac adaptations to physical exercise and address their roles in mediating the protective effects of exercise against diverse CVDs, including MI, IRI, HF, diabetic cardiomyopathy, AS, hypertension, and PH. Also, we discuss changes of circulating miRNAs in response to acute and chronic exercise. These evidences highly suggest that miRNAs could serve as potential biomarkers for exercise physiology as well as novel therapeutic targets to combat CVDs.

Mounting evidence has confirmed the roles of miRNAs mediating the beneficial effects of exercise. However, limitations of these studies should be acknowledged. First, mechanistic regulations of miRNAs in response to exercise are still unclear. The dysregulation of miRNAs in the settings of acute as well as chronic exercise may rely upon either de novo miRNA transcription or post-transcriptional processing of premature miRNAs forms [122]. Circular RNAs may act as miRNA sponge

by inhibiting miRNA activity, thus regulate cardiac adaptations to exercise [123]. Second, individuals may response differently to variable type, intensity, and duration of exercise. Thus, subsequent studies are needed to evaluate the regulation of miRNAs upon different modes of exercise across diverse populations. Third, the exact cellular sources as well as the secretion mechanisms of exercise-induced circulating miRNAs remain largely unknown. Despite that skeletal muscle function is closely related and contributes to circulating miRNAs upon exercise stimuli, other tissue or cell types such as myocardium, cardiac fibroblasts, and vascular endothelial cells should be explored as potential sources of circulating miRNAs [124]. Finally, the biological functions of exercise-induced miRNAs in physiological cardiac hypertrophy as well as their potential in CVD therapeutics deserve further explorations.

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Chapter 16
Exercise Training and Epigenetic Regulation: Multilevel Modification and Regulation of Gene Expression

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Abstract Exercise training elicits acute and adaptive long term changes in human physiology that mediate the improvement of performance and health state. The responses are integrative and orchestrated by several mechanisms, as gene expression. Gene expression is essential to construct the adaptation of the biological system to exercise training, since there are molecular processes mediating oxidative and non-oxidative metabolism, angiogenesis, cardiac and skeletal myofiber hypertrophy, and other processes that leads to a greater physiological status. Epigenetic is the field that studies about gene expression changes heritable by meiosis and mitosis, by changes in chromatin and DNA conformation, but not in DNA sequence, that studies the regulation on gene expression that is independent of genotype. The field approaches mechanisms of DNA and chromatin conformational changes that inhibit or increase gene expression and determine tissue specific pattern. The three major studied epigenetic mechanisms are DNA methylation, Histone modification, and regulation of noncoding RNA-associated genes. This review elucidates these mechanisms, focusing on the relationship between them and their relationship with exercise training, physical performance and the enhancement of health status. On this chapter, we clarified the relationship of epigenetic modulations and their intimal relationship with acute and chronic effect of exercise training, concentrating our effort on skeletal muscle, heart and vascular responses, that are the most responsive systems against to exercise training and play crucial role on physical performance and improvement of health state.

Keywords Exercise training • Epigenetic • Gene • Mechanism

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1 Introduction

Exercise is an ambient stimulus that elicits acute and adaptive long term changes in locomotor and physiological system. The changes challenge the whole-body homeostasis and mediate the improvement of performance and health state. These responses are integrative and occur both to cellular and systemic level in several tissues, and organs, as the endothelial/vascular, cardiomyocyte/heart, myocyte/skeletal muscle due or by the increase of metabolic demand of contracting skeletal muscle [1].

There is an intricate network of mechanisms that orchestrate the acute and adaptive exercise-induced response and there is much to be clarified on this issue despite the ongoing investigation. These mechanisms can be considered at several levels: related to the stimulus that triggers them, as well as the signaling pathways involved, structural level, metabolic level, and finally the mechanisms of regulation of gene expression [2].

Gene expression can be regarded as "bricks" that build the exercise-induced effects. There are molecular basis to all mechanisms involved in adaptive response exercise-induced, as muscle contraction, increased mitochondrial mass, increase of oxidative and non-oxidative metabolism, enhanced angiogenesis, cardiac and skeletal myofiber hypertrophy.

All the processes involved are mediated by several signaling events, pre- and post-transcriptional events and regulation, translation and protein processing and there are a complex molecular spatial and temporal interactions between the phases, elements and mechanisms that orchestrate the integrated response to exercise practice, also accounting genomic, ambient and exercise stimuli as intensity, duration and frequency [3].

One aspect of this spatial and temporal relationship of gene expression is the epigenetic regulation. Epigenetic is the study of changes of the gene expression independently of genotype that is heritable or dynamically modifiable. These field approaches the several DNA and chromatin conformational changes, that inhibit, increase and finally determines the developmental or tissue specific pattern of gene expression and the phenotype [4–6]. From the epigenetic point of view, the cell nucleus can be considered a chemical reactor of infinite complexity and high turnover.

The three major regulatory groups for epigenetic mechanisms are DNA methylation, histone modification, and the regulation of noncoding RNA-associated genes. The following section explains these modifications and their relationship with exercise training, performance and health status. Additionally, the following sections review on their relationship with the acute and chronic effect of exercise training focusing on skeletal muscle, heart and vascular system, that are highly responsive to exercise and crucial to performance and health state.

2 Epigenetics: History and Concepts

The term "epigenetics" was first used by Conrad Waddington in 1946 when he defined it as "branch of biology that studies the casual interaction between genes and their products". Despite its breadth, this definition opened perspective about epigenetics as modulator of gene transcription and the increase of evidence by studies resulted in currently most accepted approach, postulating that "epigenetic is the study about gene expression changes heritable by meiosis and mitosis, by changes in chromatin and DNA conformation, but not in DNA sequence" [7]. Also, these chemical modifications in DNA occur and are reversed constantly during the life span of the individual, except to those that are constitutive, that are frequently induced in an individual during the life span and can be heritable. They perform role in nucleosome assembly, mitosis, meiosis, cell cycle, transcription, recombination and repair of DNA [8–10].

Different characteristics in monozygotic twins, progressive changes in chromatin function over development and aging, are some examples of inherited phenotypic differences of immobilized DNA sequences not mutated [11, 12]. Due the epigenetic code has a highly dynamic character it is also understood that it may influence the susceptibility to diseases, especially those related to metabolic dysfunctions, cancer and cardiovascular diseases, from random environmental influences, exposure to chemical reagents, and also behavioral patterns by previous generations. This influence is also attributed to gene expression changes due epigenetic variations in coding or non-genome regions.

The exercise training induces an adaptive pattern of gene expression that improves the performance and contributes to health state [2, 7]. Epigenetic regulation regulates in part this pattern and is interesting to know how these events and their consequences can be the usable to develop exercise and therapeutic methods of intervention, capable to prevent harmful changes to current and future generation, and also minimize harmful to current generation. Also, exercise is a viable form to study gene expression patterns that antagonizes disease, elucidating about mechanisms that intermediate both situations [11–14].

3 Epigenetic Mechanisms

3.1 DNA Methylation

DNA methylation is a highly conserved to bacteria and eukaryotes and affects stability of genome, gene expression and development. These change involves covalent addition of methyl groups (alkyl derived from methane, containing one carbon atom bonded to three hydrogen atoms — CH3) to the fifth carbon of cytosine residues (5-mC) in DNA, usually at the cytosine–phosphate-guanine dinucleotides (also called CpGs islands) sites. The CpG islands correspond to genomic regions

with more than 500 base pairs in length, 55% of those are located within promoter regions in 40% of mammals genes [12, 15].

The methylation in non CPG sites is less common and regarded as aberrant, also involved in tumorigenesis and abnormal cell functions [16].

The effect that DNA methylation has on gene expression is dependent on the site, within the genome in that occur. If methyl is added to CpG islands of gene promoters the transcription is repressed, since prevents transcription factors from binding to the promoter or by inducing binding of methyl CpG binding proteins to methylated DNA [17]. Thus methylation condenses the chromatin making transcriptional machinery inaccessible. The process of methylation/demethylation exerts important role in the embryonic development and cell differentiation, to establish properties of tissue identity (Fig. 16.1).

Methylation at the promoter and enhancer regions of genes is associated with transcriptional repression, whereas the unmethylated state is regarded as permissive to transcription [18]. Inversely, there is evidence of active transcription as nucleotide within body of gene is methylated [19].

The frequency of 5-mC corresponds to less than 1% of the total number of nucleotides in the genome, smaller amount than the expected. Nevertheless, a striking feature, of eukaryotic genomes is the presence of regions methylated interposed in unmethylated regions. However, the distributions of dinucleotides CpG (cytosine-phosphate guanine) and 5-methylcytidines are non-random [20, 21]. CpG

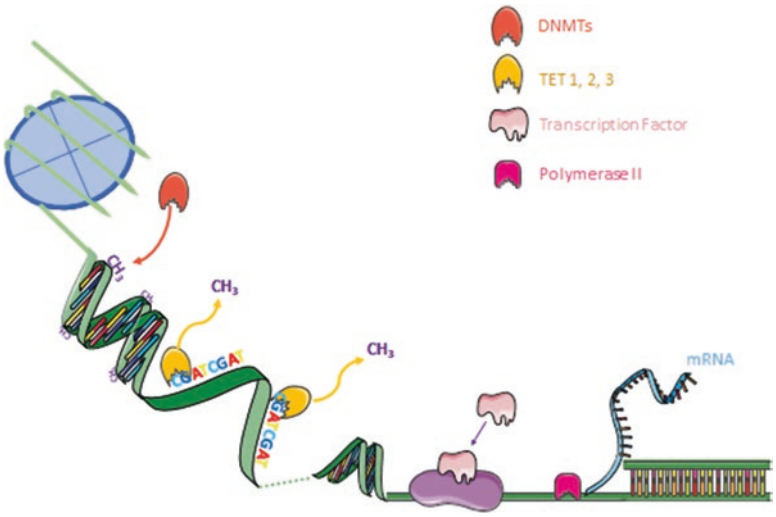

Fig. 16.1 DNA Methylation. This mechanism is due the addition of a methyl group (CH_3) to the CpGs island sites of DNA. Once CH_3 is added to promoter genes, transcription is repressed by the condensation of chromatin. DNA methyltransferases (DNMTs) are enzymes responsible for adding a methyl group to the cytosine, making transcriptional machinery inaccessible. On the other hand, TET enzymes (ten-eleven translocation) are responsible for the removal of CH_3 group, which brings the chromatin to its optimal condensation, making transcription possible once again [239]

dinucleotides, generally are methylated in normal cells, but an exception is hypomethylation of adjacent CpG regions to active genes [22].

The CPG islands also are strongly acetylated and often acetylation occurs without histone lysine 9 residue H3, leaving a chromatin in its active configuration [21, 23]. They kept unmethylated, except in genomic imprinting or located on the inactive X chromosome [24, 25], which allow a connection of proteins and enzymes that triggers transcription. In contrast, methylated CpG islands are related to transcriptional silencing [8, 26]. Around of 70% of the CpG islands at human genome are constitutively methylated, in contrast the majority of CPG island are unmethylated. Most of methylated CpG dinucleotides exist in genomic regions of transposable elements and prevent the initiation of transcription of these elements [27].

The modification of cytosine to 5-methylcytidine, prevents binding of transcription factors such as AP-2, cMYC/MYN, CREB, E2F, and NF-kB in promoter regions of transcription initiation. Although, also other proteins as MeCP-2, MDB1, 2, 3, 4 can bind these sites, that stimulate chromatin condensation and inactivate the gene [21, 23].

The methyl-binding proteins can also mediate histone modifications and direct DNA methylation cross-talk with histone modifications contribute to the DNA methylation-related transcriptional silencing [20, 28, 29].

Enzymes that catalyze group addition methyl to the cytosine molecules belong to the family of DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, DNMT3B and their isoforms, and DNMT3L. DNMT1 is the main responsible for maintaining the standards of DNA methylation during mitosis. The DNMTs3, are responsible for the *de novo* methylation of DNA molecules synthesized, being particularly important during early stages of embryonic development, since copies preexisting methylation patterns onto the new DNA strand during DNA replication. DNMT3L is an alternative splicing expressed DNMT-related protein that does not contain intrinsic DNA methyltransferase activity, but physically interacts with DNMT3a and DNMT3b modulating their catalytic activity. In combination, these *de novo* and maintenance methyltransferases seem to constitute the core enzymatic components of the DNA methylation system in mammals [30, 31].

A fourth DNA methyltransferase, DNMT2, shows weak DNA methyltransferase activity *in vitro*, and deletion of the DNMT2 gene in embryonic stem cells causes no detectable effect on global DNA methylation, suggesting that this enzyme has little involvement in setting DNA methylation patterns. The role of DNMT2 is poorly knew and studies suggest that possible that both DNMT1 and DNMT2 can functionally compensate each other [24, 32].

Another enzyme that have role in regulation of the methylation pattern in DNA is the TET (ten-eleven translocation) that oxidize 5-mC to 5-hydroxymethylcytosine (5hmC) and thus starts active removal of DNA methyl. There are three isoforms: TET1, TET2 and TET3 [33].

Studies using ESCs and iPSCs culture (embryonic and induced pluripotent stem cells) suggests that TET proteins and 5hmC abundance are involved in regulating pluripotency and differentiation in potential. Inversely of observed during ESC differentiation, reprogramming of differentiated cells into iPSCs is associated with the activation of Tet1 and Tet2 and accumulation of 5hmC [34].

Additionally, 5hmC and pluripotency is further highlighted by the existence of a cluster of binding sites for pluripotency related transcription factors upstream of TET1 and TET2: Knockdown of TET1 and TET2 causes downregulation of a group of genes that includes pluripotency-related genes including: Esrrb, Prdm14, Dppa3, Klf2, Tcl1 and Zfp42 and a concomitant increase in methylation of their promoters, together with an increased propensity of ESC cells for differentiation [35]. The Factor transcription, OCT4 and SOX2 directly control the levels of both TET1 and TET2 [34]. Importantly, TET1 depletion in ESCs downregulates pluripotency-associated genes [35, 36]. Inversely, promoters of genes that are silenced during embryo body formation lose gain 5mC at their promoters [35].

Furthermore, differentiation markers as Cdx2, Gata4 and Gata6 are induced in TET1-depleted cells. This derepression induces the potential to ESC generate extra-embryonic tissues [34, 37]. Inversely, the depletion of TET2 does not increase the differentiation potential of ESCs, and simultaneous knockdown of TET1 and TET2 appears to be less efficient in increasing the trans differentiation potential when compared to TET1 knockdown alone [34].

TET2-null mices increase their quantity of hematopoietic stem cell numbers, and myeloid progenitor cells. TET2−/− and TET2+/− stem cells have an increase in self-renewal ability in culture than wild-type cells do, suggesting that TET2 expression promotes hematopoietic differentiation. The highest levels of 5hmC of any tissue are found in the adult brain, particularly in the hypothalamus and in the cerebral cortex, but they are also high in other parts. Interestingly, as neuronal cells in the adult brain normally ceased to divide mitotically, this profile is similar that of 5-mC/5hmC that is located in gene bodies was found to be associated with higher levels of transcription, as in ESCs [38, 39]. It is possible that 5hmC in gene bodies is a more general epigenetic feature, whereas its presence in promoters may particularly be a feature of pluripotent cell types [34, 40–42].

The demethylation mediated by TET3 seems has a role in oocytes activity to reprogram somatic nuclei during cloning (somatic cell nuclear transfer) and finally, loss of 5-mC from the paternal genome in the fertilized egg correlates with an increase in 5hmC in the male pronucleus at a time when the female pronucleus remains methylated and contains low levels of 5hmC. This suggests an involvement of 5hmC in demethylation of the paternal genome. Indeed zygotes that lack TET3 increases developmental failure since fail demethylate male pronucleus and promoter regions [43–45].

The CPG islands are strongly acetylated and often acetylation occurs without histone lysine 9 residue H3 (H3K9), leaving a chromatin in its active configuration [21, 23]. They kept unmethylated, except in *genomic imprinting* or *located on the inactive X chromosome* [24, 25], which allow a connection of proteins and enzymes that start a transcript. In contrast, methylated CpG islands are related to transcriptional silencing [8, 26]. Around of 70% of the CpG islands at human genome are constitutively methylated, in contrast the majority of CPG island are unmethylated. Most of methylated CpG dinucleotides exist in genomic regions of transposable elements and prevent the initiation of transcription of these elements [19].

The studies show evidence that the methylation/demethylation state is a very important epigenetic process and that correlates with activation or gene silencing and interacts with other epigenetic regulation to orchestrate the pattern of gene expression.

3.2 Histone Modifications

Acetylation was the first posttranslational modification of histones, reported by Vincent Alfrey in 1964 [46]. After that, in later 1990s high resolution X-ray suggested that these modification was from N-terminal tails that protrude from their own nucleosome and make contact with adjacent nucleosomes [47]. In present times, is established that the N-terminal modification of histones can change the link between nucleosomes and also chromatin conformation, and consequently expose DNA sites and influence transcription, as other DNA processes as repair, replication and recombination. The changes regulate chromatin structure and also enzymatically induce remodeling from ATP to reorganize nucleosomes [4]. This section will explain about these changes and how structurally affects the chromatin and consequently the gene expression (Fig. 16.2).

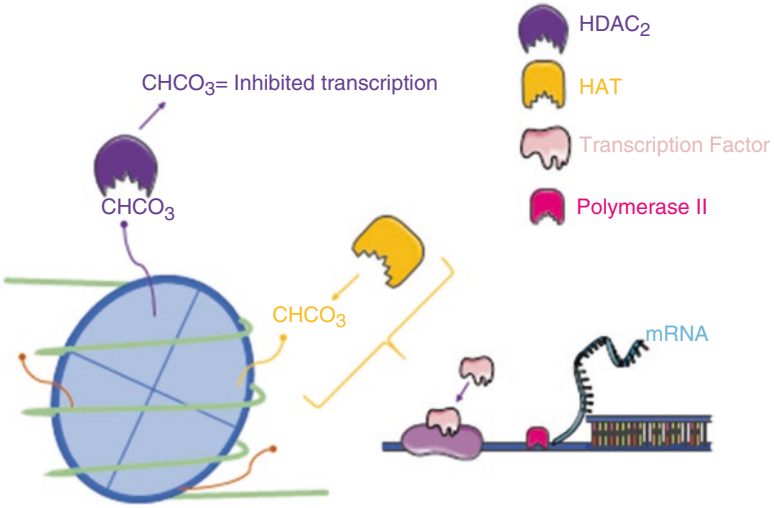

Fig. 16.2 Histones Acetylation. This mechanism consists of the addiction of an acetyl groupo (CH3CO) in the lysine and arginine residues of histones. The balance between the deacetylated and acetylated states of histones is controlled by the antagonistic actions of two types of enzymes: histone deacetylases (HDACs) and histone acetyltransferases (HATs). HATs generally are seen as transcriptional coactivators, while HDACs are considered transcriptional repressors [239]

3.3 Chromatin Structure, Nucleosomes and Histones

First, in this section, we will give a brief overview of the assembly of Chromatin to better elucidate about histone modifications and their mechanism and functions in gene expression.

Chromatin assembly of packaged units of DNA wrapped around histones isoform (H2, H3, H4) protein structures called nucleosomes. The histone core is positively charged and forms a tight structure with negatively charged DNA backbone, thereby restricting access of transcriptional factors to DNA and suppressing gene expression [3].

The nucleosome particle contains one H3-H4 tetramer and two H2A-H2B dimers and wraps two times 147 pb of DNA [48]. The histones are unable to self-assemble into nucleosomes under physiological conditions and tend to interact with DNA nonspecifically [49]. The regulation between histones and DNA are performed by histone chaperones [50] that regulate interactions between chaperones assist in assembly and disassembly by regulation of interactions. Assembly factors in complex with histone dimers are then recruited to sites of chromatin assembly by chromatin-associated proteins, where they are deposited. After the nucleosomes formation, chromatin organization is restored by chromatin remodeling complexes, which promote nucleosome spacing [48].

Summarizing the stepwise in assembly of histone proteins onto chromatin: First the Nucleosomes form from H3-H4 dimer precursors, and associate with histone chaperones that prevent nonspecific histone–DNA interactions. These chaperones hand off histone dimers to assembly factors, which are specific to the histone that recognize. Second the H3-H4 assembly factor is recruited to target chromatin regions by DNA-bound recruiter proteins, allowing the deposition of (H3-H4) 2 tetramers. Third, upon the incorporation of H2A-H2B dimers, the new nucleosome forms. Last, the spacing creates disorganization of new and old nucleosomes, that is restored by the chromatin organizers proteins [48].

Modifications to the amino acids residues in the histone proteins, notably H3 and H4 induce major changes on chromatin structure and consequently in gene expression, since alter the histone/DNA association and is more permissive to transcriptional factors binding to DNA [3]. Such modification include lysine, arginine acetylation and methylation, lysine ubiquination, serine phosphorylation, and Poly-ADP-ribosilation of histones and will be approached in next sections.

3.4 Acetylation

Acetylation consists in reversible addiction of acetyl group (CHCO3) in lysine and arginine residues in histones. Histone acetylation is a process closely linked to gene transcriptional activation, while histone deacetylation consistently results in gene transcriptional repression. Acetylation/deacetylation patterns control the

nucleosome assembly, the folding of chromatin and gene transcription, since that overcomes repressive effect of nucleosomes, and allows dynamic changes in gene transcription [51].

The balance between the acetylated and deacetylated states of histones is controlled by the antagonistic actions of two types of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). As such, HATs are generally seen as transcriptional coactivators, while HDACs are considered transcriptional corepressors [51].

The HATs neutralize the lysine's positive charge and weaken the interactions between histones and DNA, using acetyl-coA as cofactor. They catalyze the transfer of an acetyl group to the ε-amino group of lysine side chains. HATs are divided into major classes: type-A (HATsA) and type-B (HATsB). HATsB are predominantly cytoplasmic, acetylating free histones that were not deposited into chromatin. HATsB acetylate newly synthesized histone H4 at lysine 5 and lysine 12 (and some sites within H3). This pattern of acetylation is important for deposition of the histones, after which the marks are removed [52].

The HATsA are a more broad family of enzymes than the HATsB and they can be classified into three separated groups (GNAT, MYST and CBP/p300) families depending on amino-acid sequence homology and conformational structure [53]. HATsA are associated in large multiprotein complexes that play important roles in controlling enzyme recruitment, activity and substrate specificity. Each of these enzymes modifies multiple sites within the histone N-terminal tails but not only in histone tails but also in sites within globular histone core: as side chain of lysine 56 (H3), in human by hGCN5 [54]. This class functions in several transcriptional coactivators, and also has ability to neutralize positive charges, thereby disrupting the stabilizing influence of electrostatic interaction [55].

Inversely to HATs, HDACs reverse lysine acetylation, thus restoring the positive charge and repress transcription. HDACs are divided into four class and acetylate histones and non-histones protein [55].

The histones deacetylation by HDACs leads to chromatin condensation, and therefore, predominantly represses gene transcription [51]. Classified in accord to the expression patterns, cellular localization, enzymatic activity, and protein structure, mammalian genomes encode 11 members of the HDAC protein family, divides into four classes (class I, IIa, IIb, III and IV HDAC). Class I, II, and IV HDAC contain a Zn2 + − dependent deacetylase domain [55, 56].

Class I are expressed ubiquitously, localized in the nucleus and presents high enzymatic activity. Their structures are simple, consisting of the conserved deacetylase domain and short amino- and carboxy-terminal extensions. HDAC1, 3 5 and 8 are members of this class.

Class II has large N-terminal extensions with conserved binding sites for the transcription factor myocyte enhancer factor 2 (MEF2) and the chaperone protein 14–3-3, which increase their responsive signal. Consecutively, occur phosphorylation by kinases, such as calcium/calmodulin-dependent protein kinase (CamK) and protein kinase D (PKD), and these HDACs bind and shuttle from the nucleus to the cytoplasm [4]. This class show restricted expression patterns. HDAC5 and HDAC9

are highly expressed in skeletal muscle, heart and brain [57]. HDAC4 is highly expressed in the brain and growth plates of the bones [58], and HDAC7 is enriched in endothelial cells and in T-cell precursors derived from the thymus. The class IIa HDACs recruits class I HDACs through their C-terminal HDAC domain, which probably accounts for a portion of their repressive activity [59]. In addition, the regulatory domains of class IIa HDACs interact with transcriptional repressors, such as C-terminal-binding protein (CTBP) and heterochromatin protein 1 (HP1) 37, 38, 40 performing role as adaptors to nucleate multiple types of transcriptional regulators and to confer signal responsiveness to downstream target genes [40].

Class IIb HDACs are constituted by HDAC6 and HDAC10. HDAC6 is the main cytoplasmic deacetylase in mammalian cells. The proteins directly affected by HDAC6 are cytoskeletal proteins such as α-tubulin and cortactin, transmembrane proteins such as the interferon receptor IFNαR, and chaperones This isoform has two catalytic domains and a C-terminal zinc finger [60–63]. HDAC10 are enriched in cytoplasm and highly expressed in mammalian tissue and interacts with HDAC3 but the role of this interaction remains to be clarified [10, 60].

The Class IV has only one isoform: HDAC11. Little is known about its role, although it is enriched in several tissues: as brain, heart, skeletal muscle, kidney and testis. HDAC11 has a catalytic domain homologous to HDACI and II classes with short N- and C-terminal extensions [64].

In contrast, class III HDAC, also called sirtruins, characterized by NAD + − dependent deacetylase domains [65, 66]. The sirtruins are divides into five subclasses (I–IV and U) based on the phylogenetic conservation of a core domain of 250 amino acids [67]. The enzymatic activity of this class is linked to the energy status of the cell due its dependence of NAD+ [68]. Thus this class in mammals have an important role in regulation of metabolic functions, especially the class I Sirtruin I. Sirtruins have roles in metabolic homeostasis during fasting and caloric restriction by acetylation level and activity of key metabolic targets PGC-1a, FOXO1, FOXO3, NF-kB, MEF2, p53, 300 e MyoD [69].

The activities of HATs and HDACs are very important for gene transcription, since the dynamics of active genes presents high levels of acetylation turnover. It is thought that this dynamics is orchestrated by a first recruitment of HATs by transcriptional activators leading to high levels of acetylation and that HDACs are also recruited to the active gene and act as part of their global function. Also, is possible that due to the activity of HATs being more stronger then HDACs, the balance of acetylation and deacetylation changes is to more acetylated state. Also can occur overlapping specificity of HATs and HDACs, as most lysines are acetylated by HATs, but some lysines are stronger targets of deacetylation by HDACs. Thus, a combination of two mechanisms determines the functional outcome of histone acetylation and deacetylation. Also the modification exerts functions by two ways: the acetylation/deacetylation is coordinated or redundant and dictates function and second, acetylation/deacetylation of specific residues has alone functional effects [51]. Concluding, the functional state of acetylation and protein binding at a gene requires a complex analysis of HAT and HDAC recruitment, histone acetylation. Transcription profile is highly dynamic state, very sensitive to methylation/acetylation relation and other epigenetic modifications during gene activation and repression. In this

way, is possible to have a comprehensive view of the various layers in which acetylation, deacetylation, and other epigenetic and histones modifications regulate gene activity (Table 16.1).

3.5 Other Histones Modification

Although acetylation is the best characterized histone modification, This section approaches other modification that influences chromatin structure and thus gene expression: Phosphorylation, Deamination, β-N-acetil-glucosamine, Poly-ADP-ribosylation, ubiquination, sumoylation, histone tail clipping, isomerization.

Phosphorylation This change is highly dynamic, and occurs on serine, threonine and tyrosine, and not exclusively in the N-terminal histone tails but in core, as the phosphorylation of H3Y41 exerted by JAK2 [70]. This reaction is catalyzed by histone kinases of four enzyme families with ATPase activity (switching defective/sucrose no fermenting – SWI/SNF, imitation switch (ISWI), chromo domain helicase DNA binding (CHD) inositol requiring 80 (INO 80), that transfer a phosphate group from ATP to the hydroxyl group of the target amino-acid side chain. The effect is addition of negative charge to the histone that influences the chromatin structure. For major part of these enzymes remain unclear the site which the kinases exerts their effects and is possible that chromatin bound factor binds to DNA to assist the interaction. An exception is the mammalian MAPK1, that has an DNA-binding domain with which it is tethered to the DNA [71]. The phosphatases that dephosphorylate the sites in histones are less known, although is thought that there are high phosphatase activity within the nucleus due rapid histone phosphorylation [72, 73].

Deimination This irreversible reaction is catalyzed by the peptidyl deiminase PADI4 and consists the conversion of an arginine to a citrulline, neutralizing the positive charge of the arginine and thus exposing sites in DNA to transcription [74, 75].

β-N-acetyl glucosamine This histones modification occur in serine and threonine side chains with single β-N-acetyl glucosamine (O-GlcNAc) sugar residues and is catalyzed by O-GlcNAc transferase, consisting in the transfer of the sugar from the donor substrate, UDP-GlcNAc, to the residue. The modification occur in H2A, H2B and H4, is highly dynamic and rapidly reversible by β-N-acetylglucosaminidase (O-GlcNAcase) [76].

ADP-ribosylation This modification is reversible and consists in addiction of ADP molecules on glutamate and arginine, that correlates with relaxation of chromatin [77]. These reaction is catalyzed by poly-ADPribose polymerase (PARP) and reversed by the poly-ADP-ribose-glycohydrolase family of enzymes. PARP-1 activity induces to high acetylation core histone and its ribosylation in the HK4me3 inhibits its demethylation and excludes H1 making promoters of genes accessible [78, 79].

Addiction of only one ADP molecule is catalyzed by mono-ADP-ribosyltransferases on H2a, H2b, H3 and H4, core histones, and also in the linker H1. These modification are related with the pathway of DNA damage [77].

Table 16.1 Other epigenetic modification, localization, effector enzymes and effect on transcription

Modification	Reaction	Localization	Enzyme families	Transcription
Metylation/Demethylation	CH3	CPGislands	DNMT/TET	⇩⇧
Acetylation/Deacetilation	CHCO3	H. core and tail	HAT/HDAC	⇧⇩
Phosphorilation	PO4 by ATP	H. core and tail	SWI/SNF, ISWI, CHD, INO 80	⇧
miRNAs	binding	mRNA	–	Postranscriptional
IncRNAs	Coating Sponge	DNA, mRNA	–	⇩⇧
ADP-Ribosilation	ADP	Histones core	PARP	⇧
Ubiquitination	Ubiquitin	Histones core	E1, E2, E3 ligases	⇧
Sumoylation	small protein Like -ubiquitin	Histones core	E1, E2, E3 ligases	⇩
Tail-Clipping Histones	Removal of amino acids	H. Tail	Cathepsin L	?
Isomerisation	Cis-Trans Proline	H. Tail	Proline peptidyl isomerase	⇧
β-N-acetyl glucosamine	β-N-acetyl glucosamine	H. Core	O-GlcNAc transferase β-N-acetylglucosaminidase	⇧
Deimination	Arginine to Citruline	H. Tail	deiminase PADI4	⇧

CH3 methyl group, *CHCO3* Acetyl group, *PO4* Phosphate group, *ATP* Adenosine Triphosphate, *ADP* Adenosine Diphosphate, *H.* Histone, *DNMT* DNA methyl transferase, *TET* ten-eleven translocation, *HAT* Histone acetil transferase, *HDAC* Histone deacetilase, *SWI/SNF* switching defective/sucrose no fermenting, *ISWI* imitation switch, *CHD* chromo domain helicase DNA binding, *INO80* inositol requiring 80 (INO 80), *PARP* Poly ADP ribose polymerase, *ADI4* Protein-arginine deiminase type-4

Ubiquination and Sumoylation This covalent modification is larger than others and highly dynamic, consisting in the attachment of Ubiquitin, a polypeptide, covalent to histone lysine via the sequential action of three enzymes: E1, activator of Ubiquitin, E2, conjugator of Ubiquitin and E3-ligation enzymes. The modification is removed via the action of isopeptidases [80]. Although the sites H2A and H2B. H2AK119ub1 are related with gene silencing, and H2BK123ub1 with transcriptional initiation and elongation little is known about this modification [75, 81]. Sumoylation is addiction of small molecules like-ubiquitin lysine in the H2A, H2B, H3 and H4. This modification is considered be repressive since, antagonizes acetylation and ubiquination in the side chain of lysine [82–84].

Histone Tail Clipping This modification consists in remotion of several amino acids residues of histone N-terminal tail in Histone that they reside [85–87]. In mammals the mouse enzyme was identified as Cathepsin L, and cleaves the N-terminus of H3 during ES cell differentiation Histone tail clipping is also related with DNA damage and show a consequent modification in acetylation and methylation patterns, but direct relation with transcription and gene expression in human is not stablished [87].

Isomerization This modification is not covalent and consists in the interconversion of proline between the cis and trans conformations, being catalyzed by isomerases [88, 89]. Recently, this modification is related to aspartate residues in brain mices, being D-asparagyl related to activation of chromatin and increased transcription activity.

3.6 Non Coding RNAs

Nowadays is clear that Non-coding RNAs (ncRNAs) have different regulatory functions in Eukaryotes, including in mammalians. Recently, in last decade, ncRNAs have been implicated also in epigenetic mechanisms, as transposon activity and silencing, paramutation, variegation and X-chromossome inactivation. The ncRNAs are also able to direct the DNA methylation and histone modifications and thus related to gene expression control in complexes organisms [90].

The ncRNAs are RNAs molecules that do not encode proteins, but have regulatory functions. According to their size they can be divides into small and long ncRNAs [91]. These small ncRNAs, includes single strand endogenous microRNAs, siRNAs (small interfering RNAs) e PiRNAs (Piwi-interacting RNAs) (17–29), that differentiates in enzymatic process and Argonaut recruitment in their biogenesis. Since all are negative regulators of translation step in protein synthesis, they play important roles in numerous cellular and tissue processes, as apoptosis, proliferation, differentiation, growth, DNA damage, and pluripotency [92]. Currently there are 2603 mature sequences of small ncRNAs discovered stored at data base airbase 21 (mirbase.org). They act by the coupling in the messenger RNA (mRNA) transcript from a gene and initially was believed that only coupled in 3′ UTR (untranslated region) regions. Today we know that there are several functional sites to small non coding in cell as 5′ UTR region and that there are miRNAs interactions

with others microRNAs and proteins. The small ncRNAs are "promiscuous" molecules, since they have hundreds to thousands of targets and several can act in one target simultaneously to effective their function. Small non coding RNAs have multiple pairing possibilities in sites within their target gene. To approach exactly their functional target genes and "wave" effects remains an important challenge to researchers [93, 94].

Small Non Coding RNAs In mammalian, the small ncRNAs are not directly related with epigenetic regulation, although in disease, aberrant expression of microRNAs and their cluster can alter the global DNA or chromatin state by negatively inhibition of DMNTs 3 and 1 and these regulation [95–97].

The loss of a crucial component in biogenesis of small ncRNAs, Dicer, that processes long RNAs, was able to induce aberrant accumulation of long non-coding RNAs in centromeres and consequently there was loss of histone H3 lysine 9 methylation (H3K9me), which was detrimental to the functions of the centromere [98, 99].

There are silencing protein complexes (RITS, RISC), guided to small ncRNA that acts in pairing between centromeres, complementary DNA sequence and in negative regulation in targets messenger RNA (mRNA) [92, 100, 101]. These complexes also have methyltransferase activity to repetitive regions to methylate histone H3 at lysine 9 (H3K9me). This modification is able in turn recruits chromodomain-containing proteins, such as Chp1, Chp2, and Swi6, to initiate the spreading and establishment of heterochromatin domains. RITS is able to interact with another complex called the RDRC (RNA-dependent RNA polymerase complex), that Rdp1 and Dicer activity and have RNA processing capacity, showing interaction between small ncRNAs biogenesis and epigenetic modification that formats heterochromatin structure at the centromere [102].

The Argonaut 4, other protein involved in maturation and function of small ncRNAs, has the role direct siRNA to the targets and simultaneously histone and DNA methylation [103].

The piRNAs recruit repressor factors HP1a and Su(vary)3–9 to specific genomic loci to and consequently repress RNA polymerase II transcription [104, 105]. PiRNA binds to Piwi protein complexes to the promoter region of the repressor factor CREB2 in nervous cells and mediate its memory-related DNA methylation [106].

These findings show evidence that small ncRNA molecules and machinery have roles in epigenetic regulation. Further mechanistic studies of small ncRNAs involved in this process may show others roles that remain unclear and elucidate about epigenome interactions [91].

Long Non Coding RNAs The lncRNAs can range their length from few hundred to 100 kilobase species. Evidence now suggests that large non-coding regions of the human genome are transcribed during normal and diseased cellular function. lncRNAs can express from introns, exons or intergenic regions [28]. They can be divided into five categories: (1) Sense, (2) Antisense lncRNAs that are transcribed in the opposite direction of protein-coding genes and have partial overlap with genes. (3) bidirectional when its expression and of neighbor coding transcript is initiated in close genomic proximity, (4) Intronic when is completely within an

intron of a second transcript (can be precursors by smalls ncRNAs) (5) Intergenic lncRNAs reside in intergenic regions without overlapping gene [107].

The versatile lncRNAs are implicated in epigenetic gene regulation by several forms that are only recently clarified. Initially implicated in two heritable epigenetic processes, Inactivation of X Chromosome and Imprinting, nuclear roles, lncRNAs also has been implicated in gene regulation as CERNA (Competitive Endogenous RNA). There are lncRNAs that exerts roles in nucleus and cytosol. In the nucleus, lncRNAs are able to recruit and bind complexes (including chromatin regulation and transcriptional machinery proteins as RNA polymerase) that regulate directly gene expression in promoters and gene loci and also directly bind in DNA to promote *cis* and *trans* activation. Additionally, the lncRNA binding at DNA sites influenciates acetylation and methylation pattern in adjacent sites [108, 109]. In cytosol lncRNAs are able to bind mature sncRNAs and inhibit their function and also "coating" tertiary structure of transcription factors and splicing factors [108, 109].

Concluding this section, there is evidence that the several mechanisms of epigenome "cross talk" to regulate gene expression and consequently the adaptive/compensatory phenotype required in life situation, as health/disease, development/growth. The adaptive response to training includes several signaling pathways to induce hypertrophy, angiogenesis, and metabolic gains. The signaling pathways recruit activator and repressor factors that influence the pattern of gene expression and effective the response. Thus, is not amazing that epigenetic regulation is a multilevel regulation that may orchestrate the exercise-induced response. In the next sections we will approach about the epigenetic regulation involved in exercise response in the skeletal muscle, heart and endothelial tissue.

3.7 Epigenetic Regulation, Exercise and Heart

Epigenetic events such as DNA methylation, histone modifications and microRNA regulation play an important role in the programming gene expression, in cardiogenesis and are crucial in correctly development of the heart after birth [110, 111].

Epigenetic changes are strongly influenced by lifestyle. It is known that the type of diet and physical exercise can lead to epigenetic alterations [112]. Recent studies have shown that physiological stress, promoted by physical exercise, can be determinant in epigenetic variations in myocardium [113]. In view of this, numerous researchers have focused on studies epigenetic related to the increase in phenotype variability in individuals who practice aerobic and resistance training, including epigenetic changes that can be transmitted during fetal development due to physical exercise [114–116]. It is believed that, especially, the exercise habits of pregnant women during the gestational period, can significantly impact the cardiac metabolism of the child [117]. This impact results from the binding of compounds in certain genes altering their expression which could influence future adaptations to exercise in adult life [118]. This may explain why many studies show different adaptations in the heart of individuals undergoing the same physical training [119].

These studies show evidence that the heterogeneity are not only linked to gene patterns but also linked to epigenetics alterations [120].

There is a strong evidence to epigenetic impact in a set of morphological and functional adaptations with exercise training in cardiac adult life [121, 122]. Historically, the study of the changes in the base sequence of DNA, cardiac transcriptional and translation processes and intracellular pathways signaling has been very informative in understanding the array of the events in myocardium to exercise training [123, 124]. Recently the rapidly evolving field of cardiac microRNAs has further broadened our understanding of cardiac response to exercise, however, there is still little understanding of other epigenetic alterations [111, 125]. In this section, we will describe epigenetic cardiac and their role in controlling cardiac response to aerobic and resistance training.

3.8 Aerobic Exercise

Aerobic training is well known to promote beneficial adaptations in the myocardium that includes cardiac hypertrophy, cardiac metabolism control, improvement in contraction and relaxation, formations of new blood vessels and decreased collagen content, improved myocardial antioxidant capacity, and decreased mitochondrial dysfunction and has been shown to prevent cardiomyocyte apoptosis [126, 127].

In recent years it has been demonstrated that the development of these hypertrophic phenotypes is closely linked to changes in regulatory regions of DNA. Epigenetic processes responsible for controlling the methylation and acetylation of chromatin through histones have been demonstrated in the heart. In addition, a class of noncoding RNAs has been shown to play an important role in the control of hypertrophic processes of the heart [105, 128].

The eccentric hypertrophy due to volume overload is characterized by addition of sarcomeres in series and longitudinal cardiomyocyte growth. The phenotype of this remodeling is typically related to exercises, such as running where greater volumetric overload is required. The left ventricle remodeling induced by physiological stimuli leads to preserved or even enhanced left ventricle function [114, 129].

On the other hand, cardiovascular diseases associated with the pathological cardiac hypertrophy phenotype generate exponential searches for pharmacological and non-pharmacological therapies for the prevention and treatment of this phenotype. Some studies in the last decades have suggested that the manipulation of HDACs may be interesting therapies, since its interaction with transcription factors and histones seems to regulate this phenotype of cardiac hypertrophy [130–133]. This gene regulation given by epigenetic mechanisms seems to play a key role in the development of the heart and its adaptation to stimuli generated in the myocardium in the postnatal period [134]. As already described, histones are modified by several mechanisms, which may result in the activation or suppression of gene expression.

3.8.1 DNA Methylation

To heart, physical exercise seems offers an epigenetic regulation that holds benefits with several health domains [115, 127, 135]. The exercise promotes consistent cardiovascular benefits but yet the involvement of methylation mechanisms remains to be completely elucidated. There are several studies involving physical exercise and cardiovascular health improvement but few implicating methylation [136–138].

Denham et al. applied an exercise training consisting of sprint interval training, showed that the increase of cardiorespiratory fitness of 12 healthy young men participants and the improvement of their maximal running performance was concomitant with a decrease of low density lipoprotein concentration and genome-wide DNA methylation changes in their sperm. Several CpG island and gene promoter regions were demethylated after exercise, indicating increased genome-wide transcriptional changes, including epidermal growth factor (EGF) that presented reduced gene expression. MicroRNAs miR-21 and miR-210 locus (MIR21 gene) changed DNA methylation, which induced their expression in other genes involved in improvement of cardiovascular function [139]. Concluding, exercise training is able to change the gene expression to promote health and prevent disease and there is evidence that methylation is involved in this adaptive process, that provides contributions to respiratory and cardiovascular health and regeneration. Exercise, as epigenetic regulator, implies the potential to counteract pathophysiological processes, and health-related changes in skeletal muscle, cardiovascular cells and other [7]. The underlying molecular mechanisms, as methylation regulation remains to be completely clarified, as their relationship with populations, dose-response, modality, intensity of exercise.

3.8.2 Histones Acetylation

HDACs are the most studied class of regulatory enzymes in relation to the epigenetic mechanisms related to the phenotype of cardiac hypertrophy. Studies with animals such as that of Zhang et al. (2002) show the participation of these epigenetic mechanisms related to cardiac disorders [133]. In 2002 this group published a striking article in the journal *Cell* where they demonstrated that two class II HDACs are responsible for controlling the phenotype of cardiac hypertrophy by interacting with myocyte enhancer factor 2 (MEF2), a transcription factor that activates several genes of the genetic load fetal heart disease [133]. In this study mutant mice were created for the HDAC9 gene, being refractory to the phosphorylation of HDAC kinase, thus preventing the action of HDAC9 as a suppressor of pro-hypertrophic transcription factors [133]. Still, these young animals, in the absence of stress, did not show any difference in cardiac function and morphology in relation to the controls, however, with aging or pressure overload or stimulation of calcineurin (an important activator of pro-inflammatory pathways and pro-thrombotic); these animals had a pronounced phenotype of pathological cardiac hypertrophy. The authors correlated this hypertrophy with an over activation of MEF2. Thus, they conclude in

this study that class II HDAC may act in the adult heart as suppressor of fetal load genes and its manipulation may serve as a potential therapeutic target [133].

Later in 2004, this same research group, published a new study showing once again the role of these class II HDACs as suppressors of pathological cardiac hypertrophy [130]. In this study they created a mutant animal for HDAC5, which as well as the HDAC9 deficient also spontaneously with aging had a pathological hypertrophic phenotype. To further substantiate the role of these HDACs as controllers of the cartilage remodeling process, the authors created a double mutant animal for both HDACs (HDAC5 and HDAC9) and a high percentage of these animals died during the embryogenesis period [130].

One of the most powerful weapons for the prevention and regression of this phenotype of pathological cardiac hypertrophy is physical training [140, 141]. Physical training has been used as an effective non-pharmacological tool, however little is known about its role in epigenetic mechanisms in the heart. In a recent study by Soci et al. (2016), animals were submitted to an aerobic swimming training protocol that mimics volume and intensity of training equated to that of an athlete [135]. The group of animals trained in this protocol showed a significant decrease of HDAC4, being a class II HDAC that is also associated with the development of pathological cardiac hypertrophy [135]. This HDAC4 is phosphorylated by calcium/calmodulin-dependent protein kinases I and II (CAMKI and CAMKII) which is an enzyme strongly correlated with pathological cardiac hypertrophy. With this study, the authors show for the first time that aerobic physical training may be able to modulate the expression of class II HDAC by regulating the gene expression of the fetal genetic load, thus functioning as a therapeutic alternative for cardiac disorders. Furthermore, in this study the exercise was able to modulate the expression of HP1β (heterochromatin protein 1β) which is a MEF2 corepressor, contributing to suppression of the expression of fetal reprogramming genes [135].

In 2007, Montgomery and colleagues published a study where they demonstrated the importance of class I histone (HDAC1 and HDAC2) for heart development and growth as well as cardiac function [132]. The authors conclude that these two HDACs perform a redundant work, since when the specific deletion of each was made, there were no differences in the development or function of the myocardium; however, when they were deleted simultaneously, there was an increase in lethality in these animals [132]. Other recent study showed that aerobic swimming training increased HDAC1 expression and decreased HDAC3 expression [135]. This data is in agreement with another study where treadmill training was used for 4 weeks, the authors also found an increase in the expression of HDAC1 with aerobic exercise [142]. In this study, the authors conclude that diabetic mice (db/db) have a compensatory mechanism between the two HDACs (HDAC1 and HDAC2), and there is a decrease in HDAC2 after the fourth week, when there is cardiac hypertrophy, showing so possibly HDAC2 is more closely linked to cardiac hypertrophy than HDAC1 [142].

3.8.3 MicroRNAs

Many miRNAs have emerged as promising therapeutic targets for cardiac disorders [128, 129, 143, 144]. In 2006, Van Rooij and colleagues published in the journal *PNAS* a signature pattern of miRNAs that are modified in the heart in response to transverse aortic constriction or expression of activated calcineurin and may play an important role for pathologic cardiac hypertrophy and for the phenotype of heart failure. In this study, of the 16 miRNAs that were selected because they were up- or down regulated in response to CT or Calcineurin activation [128]. One of the most prominent microRNAs was miRNA-195, thus they created a lineage of animals with overexpression of this miRNA. These animals showed spontaneous increase of myocytes with cardiac dysfunction from the sixth week after birth [128]. Therefore, the identification of miRNAs differentially expressed in conditions of myocardial stress as done in the Van Rooij study opens new possibilities in the search for therapeutic approaches to cardiac disorders.

In the search for these therapeutic approaches many studies have demonstrated the efficacy of physical training in modulating the expression of several miRNAs in the heart, thereby regulating its several target genes in several hypertrophic processes against pathological and physiological stimuli, under this circunstances, physical exercise is an important non-pharmacological therapy for the prevention and reversal of pathological processes [115, 116, 129, 140].

In 2015, Liu et al. presented in an elegant study that miRNA-222 is required to induce physiological cardiac hypertrophy caused in response to aerobic physical training, both swimming and treadmill. Furthermore, this miRNA seems to exert cardioprotective effect against pathological cardiac remodeling [145]. In this study two animal training models, aerobic treadmill and aerobic swimming were used to identify which miRNAs would present a pattern of expression that would induce physiological cardiac hypertrophy in both models [145]. The miRNA-222 was increased 2.1- and 2.8-fold in the swimming and running exercise models, respectively ($p < 0.003$ and 0.02), so it was selected with particular interest.

After selection of miRNA-222, the authors created a transgenic animal with overexpression of this miRNA and induced an ischemic injury in these animals. As results, they obtained that the overexpression of this miRNA caused cardioprotective effect reducing fibrotic content in relation to the control group [145].

Aerobic physical training has already been described as capable of modulating the expression of several miRNAs responsible for cardiac remodeling [115, 127, 135, 146, 147]. In 2011, Soci et al. showed that miRNA-29c expression was increased with swimming training and was negatively correlated with the expression of collagen content, improving myocardial compliance [115]. Fernandes et al. (2011) demonstrated that the same protocol of aerobic physical training of swimming was responsible for increasing the cardiac expression of miRNAs-27a and -27b and followed by a decrease of miRNA-143, which presented as direct targets components of the renin angiotensin system (RAS) Strictly related to cardiac remodeling [127]. The miRNA-126 was also correlated with physical swimming training inducing cardiac remodeling, Da Silva et al. Demonstrated that training

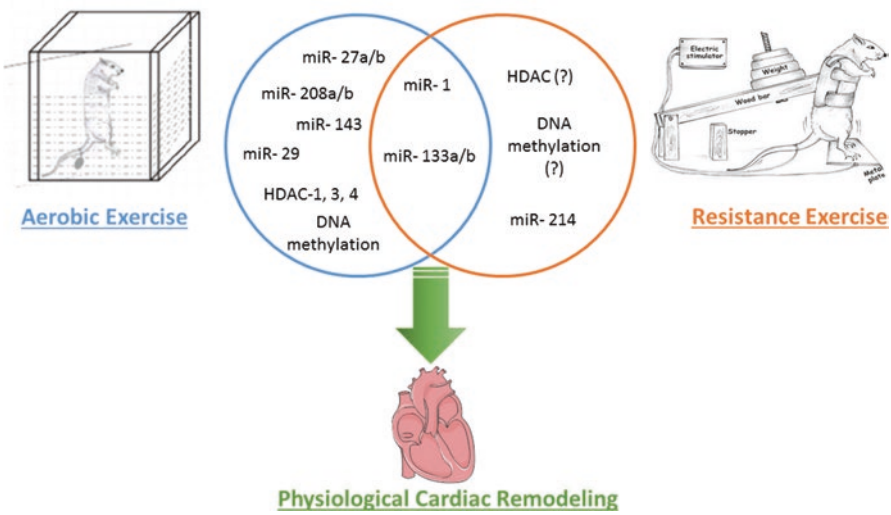

Fig. 16.3 Schematic summary of the epigenetic cardiac regulation in the cardiac remodeling induced by aerobic and resistance exercise in animal model. MiRNAs involved in aerobic training adaptive response, resistance training adaptive response and both training response. Methylation and Acetylation are known to regulate aerobic training responses, but not resistance training response. All epigenetic regulation interacts to orchestrate the physiological cardiac remodeling. MiRNAs (microRNA), HDAC. (Histone deacetylases) [148, 154, 155, 239]

induced physiological cardiac remodeling followed by increased angiogenesis, which correlated with a decrease in Spred-1, which favored an increase in pathway signaling Pro-angiogenic reactions such as Raf-1/ERK ½ [148]. In addition, the miRNA-126 also targets the PI3KR2 protein, was decreased in the trained groups, causing an increase in PI3K/Akt/eNOS pathway signaling in these groups [148] (Fig. 16.3).

3.8.4 Resistance Exercise

Several studies suggest that resistance training has beneficial effects on the cardiac morphological and contractility and can potentially be an effective treatment for various clinical conditions as such heart disease [149, 150]. It is well established, that cardiac after-load due to intermittent increases in blood pressure during resistance training induces pressure overload to the left ventricle. This intermittent pressure stimulus to the heart increases cardiomyocyte cell width and consequently increase left ventricular wall thickness. This cardiac hypertrophy features observed in weight-lifting athletes are defined as concentric and physiological [127]. On the contrary, the cardiac hypertrophy occurs in response to situations such as hypertension and valve diseases are defined as concentric and pathological [151]. Although the cardiac hypertrophy in cardiovascular system already have been established

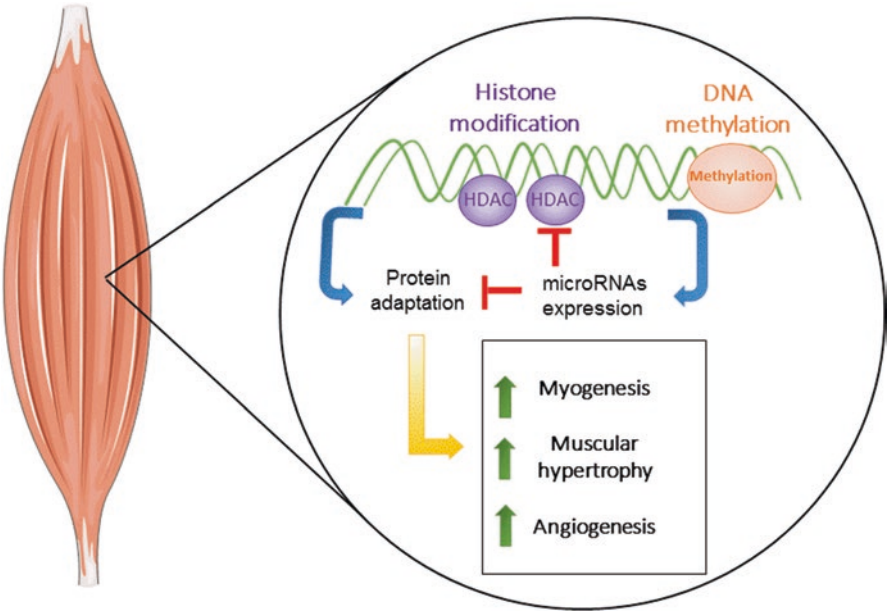

Fig. 16.4 Schematic summary of the epigenetic skeletal-muscle regulation in biological process related to exercise training. DNA Methylation, Histone acetylation and MicroRNAs interacts to regulate protein synthesis and thus skeletal muscle myogenesis, hypertrophy and angiogenesis. HDAC (Histona deacetilases) [239]

with resistance training [152], little is known about the molecular mechanisms responsible for mediating the different forms of cardiac hypertrophy (Fig. 16.4).

Resistance training-induced beneficial adaptation to the cardiovascular system was neglected by many years, thus many of the mechanisms of resistance training induced cardiovascular adaptations are still uncovered [149, 153]. One of the main problems is still the lack of models animals with similar protocols of the resistance training performed for humans. Our group and others has used an animal model of resistance training that mimic the exercise performed for bodybuilding in rats and today it is the most used model by many laboratories [154].

In 2005, our group using this animal model of the resistance training showed left ventricular hypertrophy in rats in response to resistance training [155]. The extent of left ventricular hypertrophy found in the trained group (12%) was similar to that reported in some human studies involving weight lifters training for no longer than 3 months, but smaller than that seen in other studies investigating athletes engaged in this type of exercise for more than 1 year [156, 157]. In addition, our group also investigated the morphology of single left ventricular myocytes induced after 8 weeks of resistance training. In this study confirmed that resistance training model promoted an increase the width and volume of left ventricular myocytes when compared to sedentary control animals [158].

Many researchers have focused on miRNA studies predominate in the field of cardiovascular system [159], however little is known about their expression patterns or role of the miRNA in physiological cardiac hypertrophy conditions, especially with resistance training [127]. On the another hand, in studies to analyze the cardiac miRNA expression signature of miRNA with use of the microarray platforms indicated that miRNAs are aberrantly expressed in pathological cardiac hypertrophic mouse [128]. In this regard, miRNA expression profile under either experimental or clinical conditions of cardiac hypertrophy has been revealed [160]. Studies have identified anti-hypertrophic miRNAs (miRNA-1, -133, -26, -9, -98, -29, -378, and -145) and pro-hypertrophic miRNAs (miRNA-143, -103, -130a, -146a, -21, -210, -221, -222, -27a/b, -199a/b, -208, -195, -499, -34a/b/c, -497, -23a, and -15a/b) in the heart and miRNAs that are expressed only in cardiac tissue (miRNA-1, -133a/b, -208a/b, and -499) [127]. Interestingly, in experiments with transverse aortic constriction that promotes concentric cardiac hypertrophy occurred an downregulation of the miRNA-1 and -208a while overexpression of miRNAs-208a and -499 were involved with pathological cardiac hypertrophy [161–164].

Additionally, Melo et al. observed in animals subjected the same protocol to resistance training that the isolated cardiomyocytes had an improvement in contraction and relaxation [158] and Pinter et al. showed that the improvement in cardiomyocyte contractility was due to an increase in myosin ATPase activity, the papillary muscles developing more isometric force and an enhanced Ca_2+ influx and in the trained group [165]. These results shown that there is not agreement with results from other studies that cardiac function is not altered in resistance training individuals [157]. Although, Melo et al. did not test all mechanisms, the increase in the expression of calcium regulatory proteins such as Serca 2a which, show in cells of the training group in this study, that is responsible in rat ventricular cells for 92% of Ca_2+ reuptake may partly explain the improvement the time to peak and time to half relaxation [158, 166]. From these data our group was the first to identify Serca-2a target miRNA differently expressed in cardiac left ventricular induced by resistance training. Through in silico analysis of predicted targets for miRNA, we verified a possible relationship between Serca2a and miRNA-214. Our results showed that decreased miRNA-214 levels in the trained group may explain the increased expression of Serca2a. This relationship becomes of great interest because our results show that the regulation of Serca2a by miRNA-214 occurs by resistance training [158]. However, other microRNAs may also be acting in the regulation of Serca 2a. Gurha et al., also showed that genetic ablation of miRNA-22 regulates target proteins that function as transcription factors for Serca2a expression, Wahlquist et al., showed that miRNA-25 regulates Serca2a and contributes to declining cardiac function during heart failure [167, 168]. On the other hand, the miRNA-214 may also be acting in the regulation of other contractile proteins as well as Aurora et al., reported that miRNA-214 targets both sodium/calcium exchanger 1 (NCX) and pro-apoptotic effectors of Ca_2 + signaling pathways like CaMKII and cyclophilin D [169]. Although we and others have used an animal model of resistance training to study cardiovascular adaptations data are still scarce with regard to role of the miRNA in contraction and relaxation function.

It is well-known that cardiomyocyte contractility depends on the expression of α- and β- myosin heavy chain (MHC), since MHC is the major contractile protein of the heart, and is crucial to the efficiency of cardiac performance. Studies have shown a shift from α- toward β-MHC composition of the adult heart under pathological conditions accompanied by higher expression of fetal gene reprogramming, which correlates with impaired cardiac performance [163]. Using this animal model of resistance training, Barauna et al. shown that none of the pathological cardiac hypertrophy molecular markers factor as such atrial natriuretic or α-MHC-to-β-MHC ratio, were changed in resistance training rats [155]. Interestingly, miRNA-208 encoded by the α-MHC gene, has been shown to be involved in pathological cardiac growth and up-regulation of β-MHC expression [163]. Recently, Soci et al., observed that high-volume swim training, improved cardiac diastolic function, induced cardiac hypertrophy and decreased the expression of miRNA-208a and 208b [135]. On the other hand, Van Rooij et al. (2006) showed that overexpression of miRNA-208a is required for expression of β-MHC in response to pathological stimuli [128]. Although the data indicate that different phenotypical changes observed in response to pathological state can be regulated by miRNA alterations, little is known about the mechanisms involved cardiac epigenetic with resistance training.

3.9 Epigenetic Regulation, Exercise and Skeletal Muscle

The muscular mass corresponds to more than one third of the weight of a healthy adult individual, thus the skeletal muscle is one of the most abundant tissues of the human body. The main functions of this tissue are sustentation, joint movement, heat production and caloric control [170]. The skeletal muscle is composed of cylindrical and long cells, organized in bundles and with the presence of many nuclei. This multinuclear characteristic confers to this tissue a great plasticity and that generates a rapid response to diverse stimuli such as nutritional, mechanical, hormonal and humoral [171]. These responses also generate adaptations in skeletal muscle that may be beneficial or harmful and which in turn are closely related to epigenetic factors [171].

Currently it is very clear that a number of diseases, especially metabolic chronic diseases, generate stimuli that induce harmful responses in skeletal muscle [172–174]. Muscle cachexia [175], sarcopenia [176], Inflammatory processes in the skeletal muscle [177] and microvascular rarefaction [178], are just a few examples of the responses that skeletal muscle can present as a result of pathological stimuli. All of these processes are responses that occur through innumerable molecular changes and in turn can be orchestrated without changes in DNA, for example by stimulating decompensated expression of non-coding RNAs as miRNAs, by inducing acetylation or deacetylation of chromatin and also through methylation processes [3, 171, 179, 180].

On the other hand, there are stimuli that cause changes in skeletal muscle, but these changes are beneficial. In the case of physical exercise, the muscular contractions induce the increase of the muscular mass [181], increased angiogenesis [182] and increased mitochondrial biogenesis [183]. These processes can also occur without changes in DNA [3]. Physical exercise, in turn, is also able to counteract the responses generated by some diseases in skeletal muscle, acting as a therapeutic tool.

With all that we have said so far we can understand that skeletal muscle adapts to the stimuli that individuals pass through life. Responses to these stimuli, beneficial or harmful, are linked to various signaling pathways, for example, the PI3K/AKT/mTOR that contributes to protein synthesis and hypertrophy [184], and pathways of degradation such as the PTEN and FOXO pathway [185].

The phosphorylation and activation of AKT depends on a variety of signals, such as cytokine and hormone growth factors, this activation is conditioned by the phosphorylation of PI3K [184]. Knockout animals for the AKT1 gene (AKT1 -/-) show deficiency in muscle growth [186] and mice that overexpress AKT1 result in a hypertrophic phenotype characterized by increased tissue size [187].

Another important function of AKT in skeletal muscle trophism is the regulation of gene transcription through the inactivation of FOXO, a transcription factor responsible for the transactivation of genes involved with components of the proteolytic system coordinated by the ubiquitin-proteasome system [188].

The FOXO isoforms are predominantly located in the nuclear compartment where they are expressed in the active form, but when phosphorylated, mainly by AKT, FOXO proteins are sequestered to the cytosol, where they are unable to transcribe genes involved in the process of muscular atrophy. Therefore, in muscle atrophy situations, the decreased AKT signaling pathway allows for the transcription of atrogin-1 and MuRF1, two-component skeletal muscle component of the E3 ubiquitin ligases [184, 185, 188].

Another important protein is PGC-1α, a transcriptional coactivator that regulates genes involved in energy metabolism and mitochondrial biogenesis. This protein interacts with several transcription factors from binding to the nuclear receptors [189].

The good functioning of the contractile muscular machinery is associated with the adequate expression of some protein pathways, changes in these pathways contribute to the great plasticity of the skeletal muscle and there are epigenetic mechanisms to control them. Thus, in this part of the chapter we will talk about how skeletal muscle is influenced by epigenetic mechanisms and how harmful stimuli such as chronic diseases and beneficial stimuli such as physical exercise also influence the epigenetic responses in skeletal muscle.

3.9.1 Methylation

The vitamins B6 and B12, obtained from nutrition, regulate the metabolism of homocysteine, an epigenetic product of DNA/RNA/protein methylation [190]. Hyperhomocysteinemia (HHCy) is implicated in elderly frailty and linked to vitamin deficiency, being a risk factor for cardiovascular and neurodegenerative

diseases, as well as osteoporotic fractures and complications during pregnancy. A study applied an exercise schedule to reverse HHCy-induced changes in CBS+/− mice showing greater fatigability, due to reduced ATP levels, with a lesser generation of contractile force. Molecular changes, elevated during HHcy were reversed after exercise: amount of NRF- 1, a transcriptional regulator of mitochondrial transcription factor A (mtTFA), was decreased together with mtTFA protein quantity in homocysteine treated cells, concomitant with an increase in DNMT3a and DNMT3b proteins and global DNA methylation levels in skeletal muscle [191].

Other study identified imprinted genes in skeletal muscle gene networks and observed exercise-associated DNA methylation alterations. The bioinformatics meta-analyzed only imprinted exercise-related genes, and showed that overall methylation pattern appears to be predictive to population selection and quantification of exercise. Some genes that were differentially methylated in response to exercise-activity (RB1, MEG3, UBE3A, PLAGL1, SGCE, INS) were important for muscle gene networks [192].

Voisin et al. also showed that DNA methylation decreased with exercise (60% of loci), suggesting increased gene transcription. Exercise-associated DNA methylation was stronger among older people (age accounted approximately for 30% of variation). Among older people, genes exhibiting DNA methylation decreases were in part of a miRNA-19b regulation that is tumor suppressor. Controlled exercise interventions could help the aging epigenome, especially among older patients that normally presents a several disease phenotype, including cancer propensity and cardiovascular [193].

Exercise intensity benefits for positive epigenetic changes in terms of mitochondrial biogenesis were shown by Edgett et al. Also, healthy human male subjects that perfomed interval cycling at 73, 100 or 133% presented peak power output (PPO) and post-exercise changes in gene expression of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha, a protein encoded by the PPARGC1A gene) and its regulators were estimated in skeletal muscle biopsies. Notably, increases in the mRNA levels of the regulators Sirt-1, PDK4 and RIP140 (metabolic genes) also occurred [194].

3.9.2 MicroRNAs

MiRNAs are part of the class of non-coding RNAs and there are an abundance of studies with these molecules in the skeletal muscle. MiRNAs control much of the expression of the encoded proteins in the human body; therefore, many biological processes are controlled by miRNAs in a post-transcriptional mode. Skeletal muscle together with cardiac tissue have their own set of miRNAs, such as miRNA-1, miRNA -133a / b, miRNA -206, miRNA -208a/b, miRNA-486 and miRNA-499 which are referred to as myomiRs [195], But it is to be noted that miRNA-206 is expressed only in skeletal muscle and miRNA-208a is expressed only in the heart. These miRNAs control the biogenesis, regeneration and maintenance of skeletal

muscle tissue [196]. In cases of chronic diseases it is common to find abnormal expression of these accompanied by injury to skeletal and cardiac muscle.

MicroRNA-1 and microRNA-206 are very similar. Their hairpin differ in only 3 base pairs and have the same seed region, so they share many targets and have similar functions, so they will be quoted together in this section.

These miRNAs are strongly related to muscle development, specifically there is a remarkable increase in the expression of these during the differentiation of myoblast. The high expression of these miRNAs in this period is related to the interruption of cell proliferation, an effect present in the two miRNAs. Studies inhibiting their expression show the importance of these in decreasing the proliferative phase and allowing the development of myoblasts to start [197].

Skeletal muscle satellite cells are a cell type that have an important function in regeneration and muscular hypertrophy. These are in the quiescent state until required by cellular signals that are given to the muscle after some injury. If muscle damage occurs, these cells enter the cell cycle and increase their proliferation, fuse the remaining muscle cells, differentiate and this process is one of the main ways to occur muscle regeneration; This phenomenon in turn is also orchestrated by the expression of some miRNAs among them miRNAs-1 and 206.

After an injury to the skeletal muscle occurs a remarkable decrease in the expression of the miRNAs 1/206 which is succeeded by a great increase in the expression; This phenomenon is related to the cycle of cell proliferation and differentiation. MiRNAs-1 and 206 are involved in the process of myogenesis and many of their targets have a role in proliferation and differentiation pathways, the main targets of these miRNAs regulating these processes are the proteins HDAC4, PAX3 and PAX7 [196].

PAX3 and PAX7 are important cell proliferation factors, mainly satellite cells, and these are both targets of the miRNAs-1 and 206, these data are supported by studies that have performed the superexpression of these miRNAs at very early stages of the satellites skeletal muscle cell culture and observed the premature proliferation blockade and the onset of differentiation [197].

The importance of these miRNAs during the muscle regeneration process can be observed in a study by Liu et al. that promoted the deletion of microRNA-206 and subjected the animals to muscle injuries and muscle regeneration was significantly decreased [198].

Another study by Li et al. shows the involvement of miRNAs-1 and 206 in the regulation of the cell cycle through inhibition of the CCND2 (cyclin D2) and CCND1 (cyclin D1) proteins indispensable factors for cell cycle progression [40]. The suppression of these proteins has an anti-proliferative effect and thus leading to inhibition of muscle growth and suggests a specific role of these miRNAs in decreasing the cell cycle during the differentiation process. Muscle cells with dicreased expression of miRNAs-1 and 206 result in increased anti-apoptotic factors inhibiting cell death [196].

MiRNAs 133a and 133b are extremely similar and divide many targets and function; they are related to the regulation of myogenesis, tropism and muscle regeneration.

On myogenesis, the miRNAs-133a and 133b have an ambiguous role; There is evidence that these miRNAs promote the increase of myoblast proliferation, however there is other evidence showing these miRNAs are related to suppression of proliferation and increased differentiation of myoblast. These results suggest that these miRNAs take a role in both processes, varying according to the context and phenotype. The suppression of myoblasts proliferation and the increase of differentiation occur by MAPK protein regulation. MiRNAs-133a/b, which in turn indirectly control the MAPK pathway, this miRNAs targets the FGFR1 and PP2AC proteins thus preventing the activation of MAPK. The inhibition of the MAPK pathway leads to the formation of extremely small myotubes. In this way MAPK is important in the preliminary stages of myogenesis, this protein allows the accumulation of myoblast enough to fuse and form functional myotubules [196].

However, a study by Luo et al. showed that overexpression of miRNA 133a in C2C12 muscle cells generates a significant increase in myotubes formation; one of the possible mechanisms for this phenomenon to occur is the binding of the miRNA to the FOXL2 protein, this target acts on the negative control of the protein MyoG protein responsible for the cell differentiation, that is, the miRNA 133a decreases the expression of FOXL2 leading to the indirect increase of MyoG [199].

The literature also shows that knockout animals for miRNA-133a present severe myopathies, mitochondrial dysfunction, myofibroblast morphology and cell death [198]. On the other hand, super-expression of miRNA-133a added to microRNAs-1 and 206, injected into the skeletal muscle of mice after suffering muscle damage, led to the indirect increase of MyoG and MyoD1 proteins, increasing muscle regeneration and preventing fibrosis [200].

Studies indicate that physical exercise is able to modulate the expression of several miRNAs. The work of Baggish et al. shows that exercise is able to increase the expression of several miRNAs, which are involved in the decrease of inflammatory factors, such as miRNAs-21 and 146a, and miRNAs that are involved with trophism and cardiac muscle contractility and skeletal muscle, such as miRNA-133a [201]. Moore et al. (2014) also points out that physical exercise alters the expression of miRNAs in the circulation, and some miRNAs such as -206, 1 and 21 can be used as biomarkers of aerobic training [202].

Further studies show that skeletal muscle trophism is regulated by the action of certain miRNAs, and exercise is able to control the expression of these miRNAs, for example myomiRs. The main target of miRNA-133 is the IGF-I receptor, IGF-IR; Studies performed with cells show that IGF-IR over-expression or knockdown results in the modulation of PI3K-AKT pathway phosphorylation. MiRNA-133 decreases the expression of IGF-IR and, as such, it directly contributes to the reduction of the cascade of reactions that lead to the phosphorylation of AKT, leading to decreases in the development of skeletal muscle [203]. Furthermore, a decrease of this miRNA by chronic exercise is suggested [204].

Accumulated evidence shows that physical exercise is able to modulate even the biogenesis of miRNAs by influencing the expression of proteins related to this process, for example Drosha, Dicer, and Exportin-5. The study by Russel et al. evaluated muscle biopsies of nine healthy subjects 3 hours after an acute moderate intensity cycling session. A miRNAs large scale analysis was performed on the samples and it was shown that the Drosha, Dicer and Exportin-5 proteins had their expression increased, as well as the expression of the miRNAs-1, 133a, 133b, and 181, on the other MiRNAs-9, 23a, 23b and 31 had decreased expression [205].

3.9.3 Histone Acetylation

Histone deacetylases (HDACs) remove the acetyl groups from histones; removal of the acetyl group increases the condensation of the chromatin, which in turn leads to decreased transcriptional activity. HDACs are classified as class I (HDACs 1, 2, 3 and 8), class IIa (HDACs 4, 5, 7 and 9), class IIb (HDACs 6 and 10), class III HDACs (sirtuins- sirt), and class IV (HDAC 11) [206].

The literature points out the involvement of several of these HDACs and sirtuins in the regulation of cellular trophism. Some are closely related to the process of muscular atrophy through various stimuli. The Beharry & Judge study shows that the levels of p300, Cbp, Pcaf, HDAC2, HDAC4, HDAC4, HDAC6 and Sirt1 mRNA expression increase in the process of muscle atrophy, whereas HDAC7 proteins and mRNA decrease in this condition [180]. HDAC4 proteins have already been shown to be an important trophic regulation factor, only the overexpression of this protein is capable of generating atrophy of the muscle fibers and the knockout of HDAC4 is able to attenuate the muscular atrophy promoted by denervation [207].

Epigenetic processes do not necessarily occur separately, miRNAs, for example, often present as HDAC targets [208]. From the inhibition of the HDAC4 protein through the action of the miRNAs-1 and 206 there is an increase in cell differentiation and decrease in proliferation as mentioned above [198].

Physical exercise in turn also plays a role in the modulation of HDACS in skeletal muscle. McGee et al. conducted a study to examine the effect of physical exercise on the overall histone changes in skeletal muscle in humans. The study shows that physical exercise does not generate proteosomal degradation of class IIa of HDACs, however HDAC4 and 5 are exported from the nucleus during exercise, thus removing its function of transcriptional repression. It has also been shown that there is a greater activation of the AMPK and CaMKII proteins in response to physical exercise, that are kinases that induce the nuclear export of HDAC class IIa dependent phosphorylation [206].

To conclude, physical exercise has been gaining a prominent role over the years as our society has been raising awareness through scientific studies that physical activity practice is a practical, cheap and effective therapy for the control of various diseases and to promote health. Physical exercise causes important physiological stimuli that are able to counter pathological stimuli. Skeletal muscle is one of the most important of the tissues for the practice of physical exercise, the continuous

mechanical contraction of skeletal muscle during physical activity triggers a series of signaling pathways that lead to improvement of the structure and function of muscle tissue through gene expression.

Epigenetic mechanisms that lead to beneficial adaptations of exercise in skeletal muscle have not yet been fully elucidated. MicroRNAs and HDACs are the most studied molecules, but there is still a vast field to be explored. The array technologies as "omics", certainly will propitiate more discoveries and increase the knowledge about epigenetics and physical exercise, in several other tissues and cells.

3.10 Blood Vessels, Exercise Training and Epigenetics

The vascular system has as its main function the distribution of blood flow throughout the other organs of the human body through the fine regulation of vascular resistance and blood pressure. This characteristic allows fundamental processes to the homeostasis of the organism, such as gas exchanges, the supply of nutrients, as well as the removal of metabolic residues [209]. According to its function, the vascular system is divided into conductance arteries, resistance arteries, exchange vessels, and capacitance vessels. In its structure, this system has three distinct and extremely interconnected layers. The most internal layer is called *tunica intima*; The central, middle layer, is called *tunica media*; And the outer one, called *tunica adventitia*, finally, there is the extracellular matrix that has its composition varied according to each type of vascular segment [210].

Due complexity on structure and function and intimate relationship with the other systems, the vascular system can undergo modulations against various stimuli, either pathological or physiological, resulting in the process known as vascular remodeling. Restenosis is an important pathological remodeling process, and consists in the accumulation of vascular smooth muscle cells (VSMC) or hypertrophy of the tunica media of the vessel in arterial hypertension. As a physiological response, we have the processes known as angiogenesis or embryonic arteriogenesis, and angiogenesis triggered by physical training. Through this process, the physical training is able to increase the blood supply, as well as to reestablish the microvascular network, decreasing cellular apoptosis through the increase of oxygen supply, a mechanism impaired by capillary rarefaction triggered by a series of pathologies such as arterial hypertension [211]. In the biochemical and molecular sphere, the role of nitric oxide (NO) and vascular endothelial growth factor (VEGF), as well as the balance of apoptosis stimulators and inhibitors, can be cited as the main factors responsible for the correction of endothelial dysfunction [212–215].

Over the last few decades, the understanding of physical training as one of the most important non-pharmacological measures for disease prevention and treatment has been intensified. In the same sense, the search for intrinsic responses to endothelial cells and VSMC induced by physical training has aroused the interest of the scientific community in the epigenetic study of the vascular modulations resulting

from physical training. The following will be shown studies that relate epigenetic regulation and exercise in vascular tissue.

3.10.1 DNA Methylation

Cardiorespiratory fitness is associated with improvement of endothelial and VSMC function. The ageing induces failure to balance reactive oxygen species (ROS) levels, and oxidative stress (OS). The OS is able to damage endothelial cell functions and leads to senescence. The endogenous antioxidant enzyme manganese superoxide dismutase (SOD) maintains low levels of ROS. Evidence that methylation is related with exercise effect is very recent. A study comparing aged mice sedentary, exercised and treated with the antioxidant catechin for 12 months showed that only methylation patterns in SOD promoter was lower in sedentary aged mice [216].

Hyperhomocysteinemia(HHCy), as cited in skeletal muscle section, is prevalent in aged and also hypertensive subjects [217, 218]. In blood vessels, HHCy causes imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [219]. Thus methylation is involved in these pathogenic process. A study, on aorta arteries of HHCy mice, showed that 5-aza-2′-deoxycytidine (Aza), a DNMT1 inhibitor, was able to reduce extra cellular matrix remodeling and consequently blood pressure by reduction in resistive index and wall-to-lumen ratio. Vascular response to phenylephrine, acetylcholine, and sodium nitroprusside also improved after Aza [191]. Exercise training promotes physiological vascular remodeling, arteriogenesis and angiogenesis by a set of pathways [148, 220]. Thus is not surprisingly that exercise could also alter expression and or activity of DNMTs also in blood vessel, and that methylation process is involved in beneficial exercise-induced vascular remodeling.

Exercise also increases the expression of endothelial growth factors, as VEGF, NO production by shear stress and induces endothelial progenitor cells (EPCs) in to circulation [221]. Thus, although there are few evidences that methylation is involved in vascular exercise-induced effect, further investigation is needed and relevant to be performed.

3.10.2 Histone Acetylation

It is well known that a bout of exercise increases the vascular shear stress, that can increase transcription of eNOS by chromatin remodeling on histone H3 and H4. Illi et al. (2003) established for first time the relationship between shear stress (SS) and chromatin remodeling. HUVECs were exposed to SS, and chromatin within c-fos and c-jun promoters was specifically immunoprecipitated by an antibody against acetylated histone H3 on K14. SS plus trichostatin A (HDAC inhibitor) induced histone H3 serine phosphorylation at position 10 (S10) and lysine acetylation at position 14 (K14). The results indicate that SS induces modifications of histones and show evidence of a blood flow-dependent regulation of gene expression [222].

Exercising is known to reduce blood pressure and improves wall properties by expression of eNOS and elastic fiber genes, improving cardiorespiratory fitness and SMC function, increases vascular growth factors and mobilizes EPCs, benefits MMP activity, decreasing cardiovascular risk [223–225]. Although it is well known that endothelial cell function, angiogenesis, vasculogenesis, and endothelial stem/progenitor cells are strongly affected by exercise, a direct link between histone acetylation and other histones modification in vascular tissues remains to be established.

3.10.3 MicroRNAS and Long non Coding RNAS

RNAs derived from non-coding sequences may exert an important function of regulating gene expression through small interfering RNAs, long non-coding RNAs (lncRNA) or miRNAs. The lncRNA have, in their majority, more than 200 nucleotides, being able to interact in diverse levels of the cell as in the structure, the conformation and in mechanisms of activation and cellular repression [226]. In the vascular system, lncRNA expressed in the endothelium and in the smooth muscle were recently demonstrated as regulators of both growth and endothelial function processes and the contractile phenotype of VSMC, respectively [227].

Despite the recent progress in studies on lncRNAs, the major class of RNA modulated by physical training and capable of promoting important function in the vascular system are miRNAs. These small RNA molecules are able to control about two-thirds of the protein-encoding genes, according to bioinformatics studies [213], bringing no surprises as regards their important and fundamental role in the vascular system [228].

Researchers has been demonstrating a series of miRNAs involved in physiological cardiac remodeling induced by aerobic physical training, as reviewed by Fernandes et al. [114], when the authors found evidence that physiological cardiac hypertrophy involves the regulation of miRNAs-27a and b, in addition to miRNA-143, through induction to the positive balance in the formation pathway of Angiotensin (1–7), a vasodilator, in detriment to the vasoconstriction pathway of this peptide. We also observed increased expression of miRNA-29 compared to two protocols of aerobic physical training, one of moderate and one of high intensity, in female rats. This miRNA targets the collagen gene. Thus, increased miRNA-29 expression triggers a reduction in the expression of collagen I and III, relevant for increased compliance and left ventricular function [115]. Melo et al. [116] found that aerobic swimming training was also able to promote increased expression of miRNAs 29a and 29b, with consequent prevention of increased expression of collagen I and III on the border and remote region of myocardial infarction, Suggesting positive effects of aerobic physical training in reducing the negative effects of cardiovascular diseases.

In vascular diseases, such as atherosclerosis, there are a variety of miRNAs influenced by aerobic physical training. In this pathology, physical training, as well as statin therapy, may lead to the increase of miRNA-146a, which targets the Toll-like receptor 4 (TLR4) and tumor necrosis factor receptor 6 (TRAF6), triggering, for example, a reduction in the inflammatory in vascular injury [229].

Also, in this perspective, we have that in arterial hypertension; there is a reduction in miRNA-126 microvascular expression, in addition to an increase in miRNAs-16 and miRNA-21 expressions. Considering that miRNA-126 is specifically expressed in endothelial cells, it has been described as a regulator of the migration of inflammatory cells, in addition to the formation of the capillary network and cellular survival, and is related to vascular dysfunction, inflammation and rarefaction in pathologies [148, 212, 230, 231]. One of its targets, PI3KR2 (regulatory subunit 2 of phosphatidylinositol 3,4,5-triphosphate), negatively regulates the signaling of VEGF (vascular endothelial growth factor) [148, 230, 232]. Interestingly, VEGF and Bcl-2 anti-apoptotic protein were validated as targets of miRNA-16 in endothelial cells [233–236]. The upturn in miRNA expression was also associated with decreased proliferation, migration, and formation of endothelial cell tubes in vitro [237]. In accordance with these data, miRNA-21 is also shown to be an apoptotic modulator of Bcl-2, thus suggesting a role in the regulation of angiogenic activity [233–235, 238]. In animals with arterial hypertension, aerobic physical training was able to reestablish the expression of miRNAs-126, 16 and 21, in parallel with the correction of capillary rarefaction, suggesting that angiogenesis may depend on the balance between pro and anti-angiogenesis factors through the miRNAs action [148, 182]. Thus, the role of physical training as a treatment for several cardiovascular diseases, through the modulation of miRNAs, is emphasized, presenting its important therapeutic potential.

4 Final Considerations

Epigenetics and its relationship with exercise-induced gene expression is a promising and emerging research field. Although the number of studies is increasing, much remains to be investigated and discovered about. Studies approaching about methylation, acetylation and miRNAs are more common to be found, nevertheless, the other modifications remain practically unexplored. Physical activity contributes to improve health and prevent disease, inducing skeletal muscle and cardiovascular adaption. The results show that exercise is a potent ambient stimulus to induce epigenetic regulation and also that induces a gene expression pattern that counteracts in several points of disease. These candidate genes and their forms of epigenetic regulation have potential to elucidate the several mechanisms about the exercise effect, and in long term, effective therapeutic approach, nutritional and training methods to preserve and improve health.

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Chapter 17
Exercise-Induced Mitochondrial Adaptations in Addressing Heart Failure

Jubert Marquez and Jin Han

Abstract Mitochondria are complex organelles essential for the production of energy. These dynamic, complex organelles found in every cell and tissues of the body have been well-studied in various physiological models, stressing that mitochondrial dysfunction is characteristic of pathological states, especially in cardiovascular diseases and heart failure. Since heart failure progresses due to energy deficits brought about by altered mitochondrial bioenergetics and functioning, novel ways of ameliorating mitochondrial dysfunction are being studied. Interestingly, various exercise modalities can serve as stimuli which can regulate the mitochondria in different ways, such as in the increase of mitochondrial mass and copy number, in the structural fusion and fission processes, and the removal of impaired mitochondria. Considering that there are numerous kinds and protocols for exercise, there are a number of ways exercise can affect the mitochondria as well. Nonetheless these processes affect each other to an extent, highlighting the pivotal role exercise plays in improving or enhancing the state of mitochondria during disease. This chapter will focus on how exercise of different can regulate mitochondrial processes, which could be used as therapeutic strategies in addressing heart failure.

Keywords microRNA • Cardiovascular • Mitochondria • Therapeutic

1 Introduction

Exercise training has time and again been proven to improve health, and is considered as a powerful preventive tool in the development and progression of numerous diseases by influencing adaptive changes in the skeletal muscle, including in cardiovascular diseases and heart failure. Mitochondria, which densely populate the

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skeletal muscle and produces ATP for consumption, are primarily responsible for supplying large amounts of energy during long bouts of exercise [1]. This exposure to constant stimulation from exercise trainings eventually lead to an increase in mitochondrial network and volume that allows for an even greater production of energy for the body to utilize. This increase can possibly offset disruptions in the physiological homeostasis which can result in various pathological states.

It was first discovered back in 1967 that mitochondrial biogenesis is positively affected during exercise in skeletal muscles in rat model. This study by Holloszy found that mitochondria from trained rats exhibited higher levels of respiratory control and tightly coupled oxidative phosphorylation, which was found to be related with an increase in ATp production. With the aid of advances in molecular genetics, researchers were able to improve on the study pioneered by Holloszy. More recent studies were able to expound more on the details on how exercise eventually results in increased energy production. For instance, exercise has not only been discovered to induce protein production and mitochondrial DNA (mtDNA), but it is also important in structural formation (through mitochondrial fusion and fission regulation) and degradation of dysfunctional mitochondria (mitophagy) [2]. The overall objective of performing exercise is to ensure that this would serve as a stimuli to allow the body to produce increased amounts of energy, to regulate metabolism, and to easily withstand torpor. This chapter will tackle the role each mitochondrial process plays in the progression of heart failure, how each of these processes affect each other, and how different types of exercise could target the mitochondria to aid the failing heart. (Figure 17.1 Copyright under process. Lifted from J Cell Sci 2010 123: 2533–2542; doi: 10.1242/jcs.070490).

2 Mitochondrial Biogenesis

Mitochondrial biogenesis is the process by which the mitochondria increase its mass and copy number by manufacturing and assembling (or dividing) its components. Stimuli such as exercise can initiate a cascade of cellular signals related to proceed with mitochondrial biogenesis. This triggers synthesis of nuclear and mtDNA-encoded proteins before it gets transported to its respective compartments to perform functions such as reactive oxygen species (ROS) production, mitochondrial respiration, proteins and metabolites import, or apoptosis [3]. Mitochondrial biogenesis is consequential for carrying out the normal metabolic processes of the body, resulting to an overall fitness of an individual.

However during pathological states such as heart failure, mtDNA copy number as well as mitochondrial content are significantly decreased due to downregulation of the mitochondrial biogenesis [4]. Exercise therapy is thought to reverse this by increasing mitochondria mRNA expression, protein synthesis, number, and improving functional respiratory chain [5, 6]. Previously it was found that in response to aerobic exercise, the main regulator of mitochondrial biogenesis, peroxisome proliferator-activated γ receptor co-activator 1 α (PGC-1α), is activated via 5′AMP-

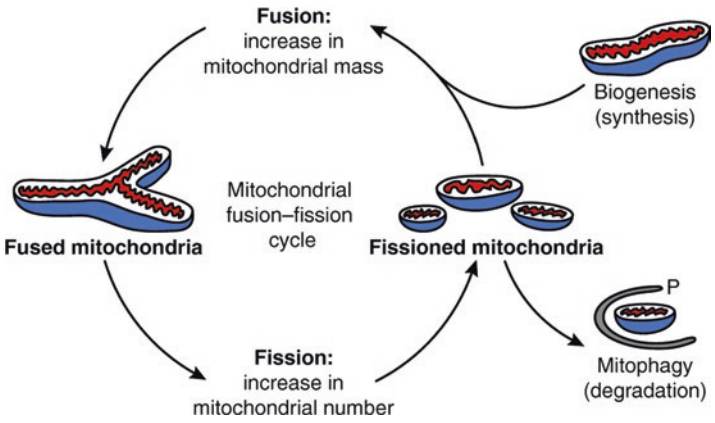

Fig. 17.1 Possible relationship between mitochondrial fusion, fission, biogenesis and degradation. An ongoing mitochondrial fusion–fission cycle allows mitochondrial functional and genetic complementation, and the proper distribution of newly synthesized mitochondria during cell division. However, an imbalance in fusion and fission events – for example, more frequent fission than fusion – might increase the total number of small mitochondria per cell if extra mitochondria are not eliminated by mitophagy. Conversely, more frequent fusion could result in large tubular networks of mitochondria. Mitochondrial biogenesis is required to compensate for decreased mitochondrial biomass resulting from mitochondrial degradation (Berman et al. 2009). Therefore, an imbalance between mitochondrial fusion, fission, biogenesis and degradation events could cause substantial changes in mitochondrial number, biomass, shape and function. P indicates a phagophore by which targeted mitochondria are engulfed during the sequestering process required for mitophagy (Copyright under process. Lifted from J Cell Sci 2010 123: 2533–2542; doi: 10.1242/jcs.070490)

activated protein kinase (AMPK) and p38 mitogen-activated protein kinase (p38 MAPK) signaling [7, 8]. By also increasing the transcriptional activity of nuclear respiratory factors (NRFs) on mitochondrial transcription factor A (mtTFA) promoter and of peroxisome proliferator-activated receptor α (PPARα), upregulation of PGC-1α has shown benefits for tricarboxylic acid cycle and ETC complexes [9, 10].

Figure 17.2 provides an example how physical exercise affects mitochondrial biogenesis. (Copyright under process. Lifted from J Cell Sci 2014 127: 4813–4820; doi: 10.1242/jcs.154229) Both PGC-1α mRNA and protein expression are significantly increased in various animal models [11–13], even in different modes of exercise training. For instance, running exercise preserves cardiac function and improves mitochondrial biogenesis among other benefits in the late stage of diabetic cardiomyopathy in mice model [14]. This increase in mRNA could be due in part to an increase in transcription activity [15]. Similarly in healthy human models, PGC-1α protein upregulation was also significantly increased during exercise for at least 24 h [11]. Concerted efforts among transcription factors such as activating transcription factor 2 (ATF2), myocyte enhancer factor 2 (MEF2), cAMP response element-binding protein (CREB), and possibly p53 could elicit transcription changes in PGC-1α as feedback to exercise stimuli [16].

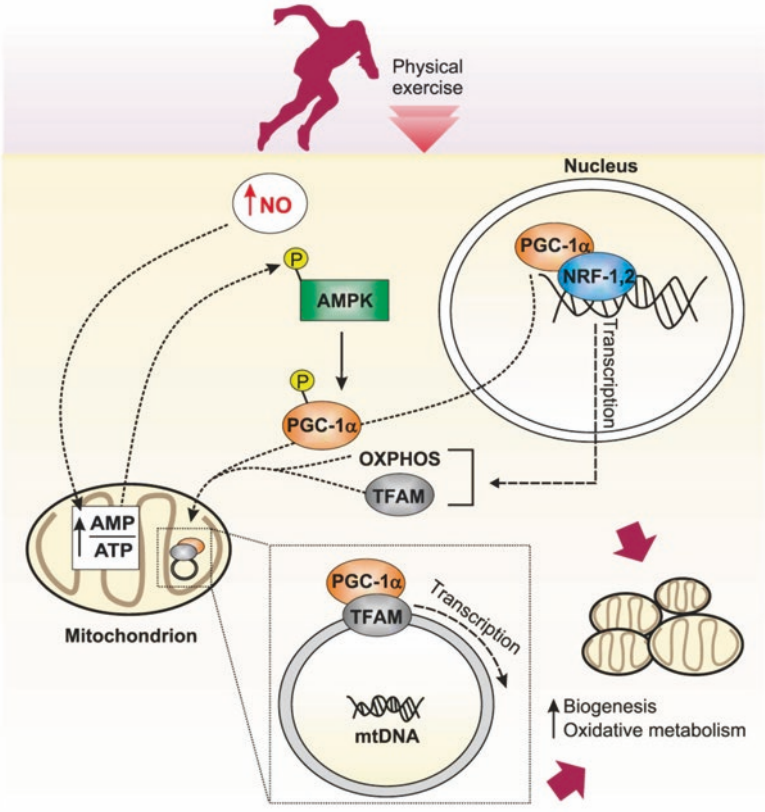

Fig. 17.2 Role of PGC-1α in coordinating the expression of mitochondrial genes during physical exercise. During physical exercise, PGC-1α interacts with the transcription factors NRF1 and NRF2 and induces the expression of nucleus-encoded mitochondrial genes, including those encoding TFAM and proteins involved in oxidative phosphorylation (OXPHOS). In parallel, the increase in NO, due to nNOS and eNOS activation, can limit mitochondrial respiration, increase the ratio between AMP and ATP and lead to AMPK phospho-activation. Activated AMPK is responsible for the phosphorylation of PGC-1α, thus mediating its translocation to the subsarcolemmal mitochondrial matrix of skeletal muscle. Here, PGC-1α interacts with TFAM on mtDNA and coactivates the transcription of mitochondria-encoded mitochondrial genes (Copyright under process. Lifted from J Cell Sci 2014 127: 4813–4820; doi: 10.1242/jcs.154229)

Bouts of exercise serve as signals which are known to activate protein modifying enzymes such phosphatases, kinases or deacetylases. These could induce conformational changes in the protein and in its activity, leading to modified mRNA expression of nuclear encoded mitochondrial proteins. These modifications aptly termed posttranslational modifications (PTMs), which are changes in a protein after translational process, can regulate mitochondrial biogenesis by targeting PGC-1α [17]. PTMs such as phosphorylation, acetylation, and methylation have been reported to have profound effect on PGC-1α activity [18]. Phosphorylation and deacetylation of metabolic intermediates have been linked to PGC-1α regulation as activated by exercise [10, 19].

3 Structural Remodeling Involving Mitochondrial Fusion and Fission

Mitochondrial plasticity is controlled by fission (division of mitochondria into units) and fusion (union of mitochondria, forming networks), and is altered under various physiological and pathological conditions including heart failure. Both processes are regulated by GTPases of the Dynamin family, albeit having opposing functions. In fission, dynamin related protein 1 (Drp1) ensures mitochondrial quality and mtDNA integrity by removing dysfunctional mitochondria through autophagy. Fusion on the other hand is controlled by mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy 1 (Opa1) [20, 21]. OPA1 mediates inner mitochondrial membrane fusion and facilitates mitochondrial inner-membrane potential apoptosis; with loss of OPA1 leading to cytochrome c (Cyt c) release and apoptosis [22]. A comparison of the mitochondrial fusion and fission process is provided in Fig. 17.3. (Copyright under process. Lifted from Front Cell Neurosci. 2016 Feb 9;10:24.)

Abnormal mitochondrial fusion and fission functions have been implicated in heart failure. For example, Drp1 is dysregulated during heart failure and Drp1-dependent mitophagy serves a cardioprotective mechanism against mitochondrial dysfunction and heart failure caused by pressure-overload [23, 24]. In fusion, OPA1 mutant heart has increased ROS, atypical calcium transient readings, lower antioxidant gene expression and mtDNA copy number, and exhibited impaired

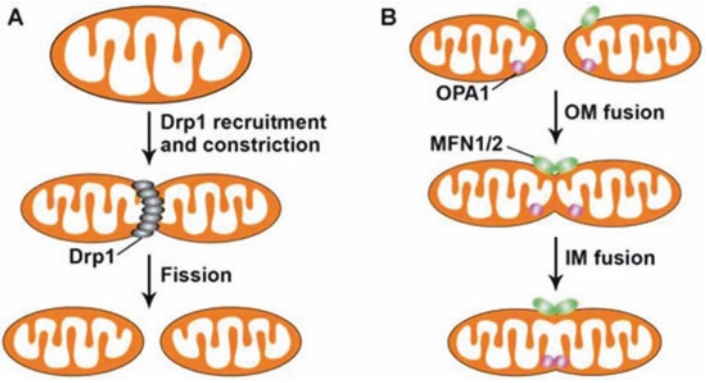

Fig. 17.3 Mitochondrial fission and fusion. Mitochondria are dynamic organelles that undergo continuous fusion and fission events to intermix their lipids and contents. (**a**) Dynamin-related protein 1 (DRP1) regulates mitochondrial fission, which consists of two steps: first, DRP1 is recruited from the cytosol to the mitochondrial outer membrane (OM); second, its assemblage on the mitochondrial surface results in constriction of the mitochondria, leading to the separation of one mitochondrion into two entities. (**b**) Mitofusins 1 and 2 (MFN1/2) at the OM and optic atrophy 1 (OPA1) at the inner membrane (IM) orchestrate mitochondrial fusion, which involves MFN1/2-mediated OM fusion of two mitochondria, followed by OPA1-directed IM fusion. Mitochondrial fusion leads to elongated and highly interconnected mitochondria (Copyright under process. Lifted from Front Cell Neurosci. 2016 Feb 9;10:24.)

mitochondrial respiration (state III and uncoupled) and complexes I and IV activity [25]. Mfn1 and Mfn2 downregulation in failing cardiac myocytes contributes to the progression of heart failure due to structural alterations and spatial reorganization of mitochondrial networks which get disconnected from ROS-induced ROS signaling [26]. Figure 17.2 at https://academic.oup.com/cardiovascres/article/109/1/6/2463396/Orphaned-mitochondria-in-heart-failure

There have been few literatures written regarding the relationship of exercise with fusion and fission regulation. However, it is generally considered that exercise can trigger different mechanisms to regulate fusion and fission processes. It was previously observed that Drp1 is increased in mice skeletal muscle during an hour of exercise and remained elevated at exhaustion. In insulin resistant obese individuals, aerobic exercise decreased Drp1 which was related with improvements in insulin sensitivity and lipid oxidation [27]. Rats under treadmill training [27] and humans who performed cycling exercise [28] increased Mfn1 and Mfn2 mRNA 24 h after exercise. Interestingly, the same study showed the regulatory purpose of PGC-1α in Mfn1 and Mfn2 transcription through ERRα. This shows how mitochondrial biogenesis, through PGC-1α, possibly plays a key role in structural remodeling involving mitochondrial fusion under the conditions of exercise.

4 Mitochondrial Autophagy

Dysfunctional mitochondria following an aberrant mitochondrial process is sequestered and degraded so it would not further affect further mitochondrial processes. This defense mechanism called mitochondrial autophagy (mitophagy) involves selective sequestration and subsequent degradation through fission. Mitophagy serves as an adaptive response by conforming itself to stress through the removal of dysfunctional and damaged mitochondria [29]. There are two well-recognized selective mitophagial mechanisms: mitochondrial serine/threonine kinase PTEN-induced putative kinase 1 (PINK1) and multiprotein E3 ubiquitin ligase Parkin, and mitochondrial receptor-mediated mitophagy involving proteins such as BCL2 Interacting Protein 3(BNIP3)/NIX [30, 31]. (Figure 17.4. Copyright under process. Lifted from Front Cell Neurosci. 2016; 10: 24.) Accumulated PINK1 activates itself inside damaged mitochondria and signals translocation and activation of Parkin through phosphorylation. Parkin is then responsible for the ubiquitination of substrates, after which polyubiquinated proteins are degraded by the proteasome, and damaged mitochondria are removed via mitophagy [32]. BNIP3/NIX-mediated mitophagy is different from Parkin/PINK1 since they serve as direct adaptors targeting the mitochondria to the autophagosome [33].

Recently the role of mitophagy as an interesting target for cardioprotection in cardiovascular disease and heart failure has been gaining attention. For example, PINK1-deficiency increased heart vulnerability to ischemia/reperfusion injury partly due irregularities in mitochondria function [34], but also allows for the easier progression to heart failure in response to pressure overload [35]. Parkin deficiency

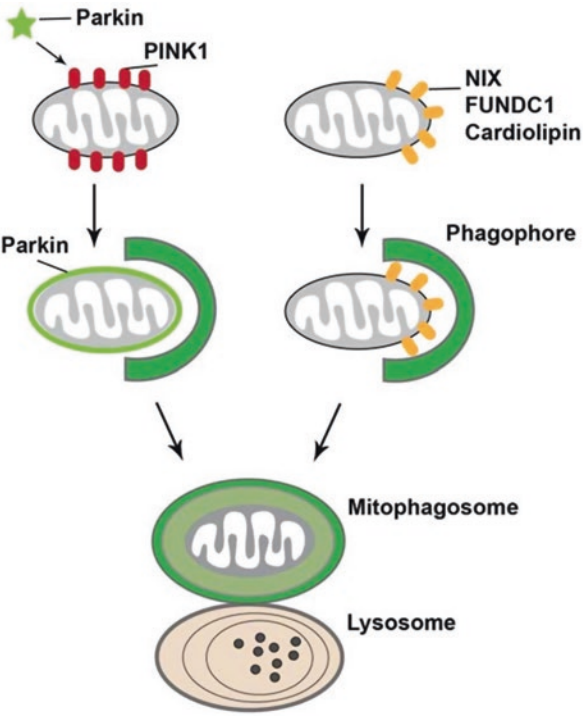

Fig. 17.4 Mitophagy. Mitophagy, which is initiated when damaged mitochondria are labeled for their subsequent recruitment into phagophore or isolation membranes, occurs through two mechanisms. First, upon loss of mitochondrial membrane potential, the E3 ubiquitin ligase Parkin is recruited from the cytosol to damaged mitochondria in a PTEN-induced putative kinase protein 1 (PINK1)-dependent manner. Parkin ubiquitinates mitochondrial proteins and causes mitochondria to become engulfed by phagophore or isolation membranes that then fuse with lysosomes. Second, outer mitochondrial membrane proteins, such as NIP3-like protein X (NIX; also known as BNIP3L), FUN14 domain containing 1 (FUNDC1), or cardiolipin externalized from the inner mitochondrial membrane phospholipid upon mitochondrial damage, bind to LC3 on the phagophore or isolation membranes, which mediate the sequestration of damaged mitochondria into mitophagosomes for lysosomal degradation (Copyright under process. Lifted from Front Cell Neurosci. 2016; 10: 24.)

also increases mortality in mice model due to the accumulation of dysfunctional mitochondria after myocardial infarction [36, 37]. In addition, Parkin mediates mitophagy during ischemic preconditioning suggesting a possible cardioprotective role [38]. On the other hand, considering that BNIP3 is highly localized in locations such as in the heart, it was found to promote mitophagy in cardiac myocytes [39]. BNIP3 and NIX both serve as mitophagy regulators in the adult myocardium, as evidenced by the accumulation of dysfunctional mitochondria in the heart with age in knockout mice of both [31].

Therefore, it is thought that enhancing mitophagy through exercise could possibly be a novel way of addressing heart failure and other disease models. However, targeting the aforementioned mechanisms has produced mixed results. In mouse

model, Parkin was increased not after exercise but by fasting alone [40]. The same group of researchers used human skeletal muscle model and reported that ultra-endurance exercise unaltered levels of PINK1 and Parkin [41]. Interestingly, acute exercise increased BNIP3 expression in skeletal muscle [42]. BNIP3 gene was also upregulated after endurance exercise [43].

5 Conclusion

Improving the overall state of a failing heart relies on the harmonious balance and interaction among the mentioned mitochondrial processes. This chapter has highlighted how exercise might be able to salvage a failing heart. A lot of novel techniques are still in its early stages and have barely scratched the surface. Hopefully in the future a more detailed approach on how exercise will exert its benefit to each of the mentioned mitochondrial processes in order to have a healthier heart.

Acknowledgements This work was supported by the Priority Research Centers Program (2010-0020224) and the Basic Science Research Program (2015R1A2A1A13001900) through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology.

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Chapter 18
Exosomes Mediate the Beneficial Effects of Exercise

Yangxin Li, Chaoshan Han, Juanjuan Wang, Jin Zhou, Chun Liang, Kasturi Ranganna, and Yao-hua Song

Abstract It is known that moderate exercise can prevent the development of cardiovascular diseases, but the exact molecular mechanisms mediating cardioprotective effect of exercise remain unknown. Emerging evidence suggests that exercise has great impact on the biogenesis of exosomes, which have been found in both interstitial fluid and circulation, and play important roles in cellular communication. Exosomes carry functional molecules such as mRNAs, microRNA, and specific proteins, which can be used in the early diagnosis and targeted therapy of a variety of diseases. Our review focus on the current knowledge on exosome production, secretion, uptake and how exercise influence exosome content. We also highlight recent research development in exosome based approach for cardiac repair.

Keywords Exercise • Exosome • Beneficial effect • Cardiovascular diseases • miRNA • HSP

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1 Introduction

It had been established that high levels of physical activity (PA) and exercise training (ET) can prevent cardiovascular diseases (CVD) [1]. A recent review article [2] summarized the beneficial effects of proper exercise on cardiac growth and angiogenesis. The molecular mechanisms of cardioprotective effect produced by exercise include activation of IGF-1-PI3K-AKT [3], NO, C/EBP-β-Cited4 [4] and AMP-activated protein kinase signaling pathways [5], as well as regulation by non-coding RNAs, epigenetic regulators [6], mitochondria adaption. Many of these actions are mediated by exosomes which can be induced by exercise [7]. The beneficial effect exerted by exosomes seems due to the release of proteins, RNAs, and especially miRNAs. Currently, exosome produced by cardiac progenitor cells [8, 9], induced pluripotent stem cells [10] and mesenchymal stem cells [11, 12] are under intense investigation as a therapeutic intervention for cardiovascular diseases.

This chapter will focus on the role of exosomes in mediating the beneficial effects of exercise, the production, secretion and uptake of exosomes, the specific molecules released by exosomes and how these molecules might be used in the prevention, diagnosis and therapy for cardiovascular diseases.

2 Exercise

Physical exercises can be grouped into two basic types based on the requirement of oxygen: aerobic exercise and anaerobic exercise [13]. Aerobic exercise (also known as cardio exercise) refers to the use of oxygen to participate in the metabolic process. Aerobic exercise is a light to moderate intensity physical activity of long duration and supported by aerobic metabolism. Examples of aerobic exercise include medium distance walking, running, jogging, cycling and swimming. Regular aerobic exercise can help to burn calories, lower LDL and blood pressure, reduce body weight and prevent stress. In contrast, anaerobic exercise refers to physical activity of short duration and not supported by aerobic metabolism. Muscles use glycolysis to produce energy and generate lactate during anaerobic exercise. Examples of anaerobic exercise include sprinting, jumping, weight lifting and other rapid bursts of high intensity exercise. Benefits of regular anaerobic exercise can help to build lean muscle mass, improve muscle strength, and lower blood sugar [14]. Up until now, only a few studies have examined the effect of egometer cycling and treadmill running on the release of exosomes in healthy male volunteers. The studies found that release of exosomes occurred during the aerobic phase. Researchers also showed that exosomes were significantly increased immediately after cycling exercise and diminished with 90 min at rest, while treadmill running triggered release of exosomes are moderate but more sustained [7]. Studies revealed that release of

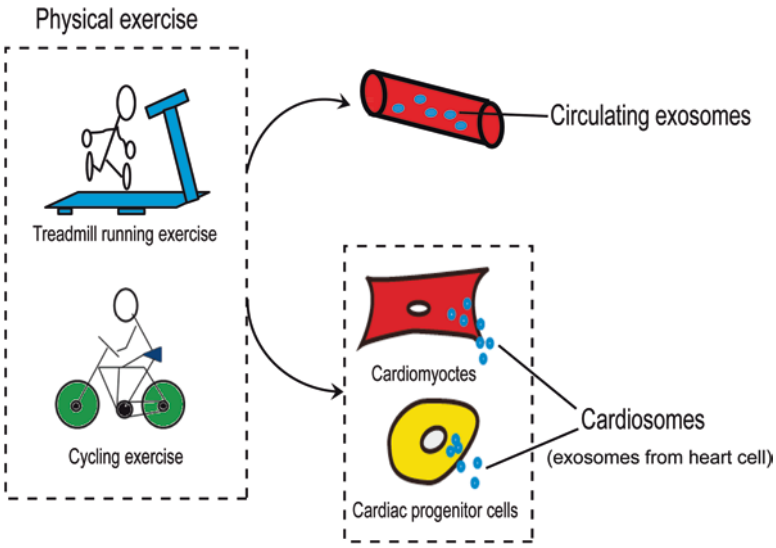

Fig. 18.1 Exercise promotes release of exosomes. The release of exosomes, which carry microRNAs, RNAs, proteins, and lipids is significantly increased in the serum and heart tissue after physical exercise, it may benefit surrounding cells via paracrine action. Cardiosome: exosomes released from cardiocytes

cardiosomes (exosomes from cardiomyocytes) is enhanced from the heart of diabetic mice with exercise as compared to hearts of non-exercise control mice. These exosomes contain microRNAs (miR-455, miR-29b, miR-323-5p and miR-466) that down regulate the expression of MMP9 and therefore prevent cardiac fibrosis [15]. Figure 18.1 depicted the effect of exercise on exosome release.

Exosome contains peptides, proteins, microRNA and DNA, and can be found in various fluid body, such as blood, urine and saliva. The expression level of certain circulating miRNA correlates cardiac function during exercise. For example, miR-1 showed a moderate negative correlation with fractional shortening, whereas miR-133a was positively related to the thickness of intraventricular septum [16]. These data indicate that exercise-dependent miRNAs may be involved in cardiac adaptation in response to exercise. Another study reported that muscle-enriched miR-486 decreases in circulation in response to acute and chronic aerobic exercise [17]. The author suggested that the reduction in circulating miR-486 may conduct glucose uptake in order to maintain muscle contraction during exercise. Researcher also revealed that the circulating miRNA signature is different during acute exercise and chronic endurance training [18]. It was shown that circulating vascular regulating miRNAs such as miR-16 and miR-126 increased significantly during and following acute exercise in young male cyclists [19]. These reports demonstrate that circulating miRNAs might be served as novel biomarkers for exercise response.

3 Exosome

It was shown that physical exercise induces rapid release of small extracellular vesicles into the circulation [7]. It is necessary to understand the mechanisms that are responsible for the formation and release of exosomes induced by exercise. While the sorting of functional molecules such as the proteins, lipids and miRNAs into exosomes have been relatively clear [20], the process that lead to biogenesis and release of exosomes induced by exercise remain largely unknown.

3.1 The Introduction of Exosomes

Extracellular vesicles (Evs) are small particles with bilayer lipid membrane released from cells into the extracellular fluid [21]. Many cell types, including cardiomyocytes, cardiac fibroblasts, smooth muscle cells, endothelium cells, mesenchymal stem cells, monocyte and dendritic cells, release exosomes [8, 22, 23]. Therefore, exosomes were widely distributed in various body fluids, including blood [24], urine [25], saliva and breast milk [26].

The exosomes are enriched in certain proteins, lipids and RNAs, suggesting that exosomes were assembled to transport unique molecules for a specific purpose [20]. Exosomes contain various types of proteins, including transmembrane proteins such as tetraspanins, endosomal sorting complexes required for transport (ESCRT), heat shock proteins, cytoskeletal proteins and trafficking proteins. Exosomes also contain small RNA species, such as microRNAs. An exosome protein and RNA database (Exo-Carta) can be found at http://www.exocarta.org/.

3.2 Exosome Biogenesis

Exosomes are small vesicles released from the endocytic compartment of living cells. The biogenesis, release and uptake of exosomes are shown in Fig. 18.2. Exosomes are originally derived from the endosome as a result of cell membrane invagination. It has been shown that different mechanisms are utilized to sort specific molecules into exosomes. The sorting mechanisms include ESCRT-dependent, lipid-dependent and specific mechanisms involving in the loading of RNA into exosome (Fig. 18.3).

There are several ways that proteins can be uptake by exosomes. ESCRT complex is composed of several subcomplexes that work coordinately to produce intraluminal vesicle (ILV) budding. Ubiquitinated proteins are recognized by ESCRT-0, which then recruits ESCRT-I, ESCRT-II and ESCRT-III. Once assembled, ESCRT-III requires activation of ATPase Vps4 (vacuolar protein sorting 4) to provide energy in order to detach from the membrane [20]. Some proteins are incorporated into

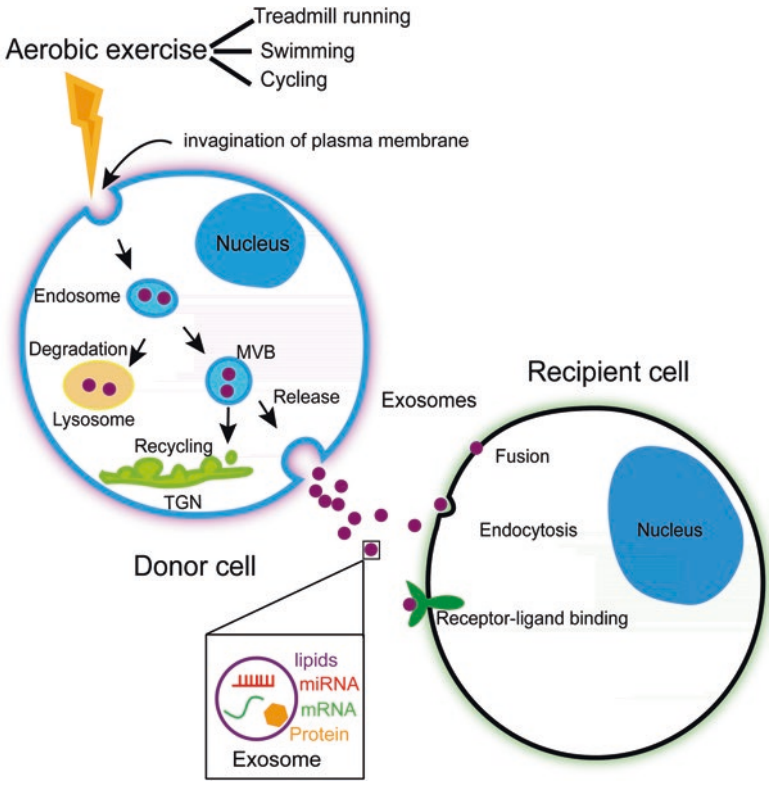

Fig. 18.2 Exosome biogenesis, secretion and uptake by the target cells. During exercise, endosome is formed through invagination of the plasma membrane and then formation of multivesicular body (MVB), which contain exosomes. The exosomes can be secreted into the extracellular environment, or the MVBs can fuse with lysosomes for degradation or recycled to the trans-Golgi network (TGN). Exosomes can be taken up by cells by binding to surface receptors, internalized through endocytosis, or fused with cell membrane

exosomes via ESCRT-independent pathway. For example, proteolipid (PLP)-positive exosome secretion is dependent on ceramide.

Exosomes are enriched in saturated lipid molecules such as cholesterol, sphingomyelin, phosphatidylcholine and phosphatyletanolamine, which suggest that the lipids sorted into exosome are also possessed via specific mechanisms. Most of saturated lipid molecules, the lipase that generates lipid, transport protein of those lipid and membranes proteins are involved in lipid-dependent way [27].

RNA sorted into exosome is also mediated via specific pathway. There are several potential pathways for sorting miRNAs into exosomes. These mechanisms include: (1) The neural sphingomyelinase 2 (nSMase2)-dependent pathway. MiRNAs are released through a ceramide-dependent secretory machinery and the biosynthesis of ceramide is regulated by neutral sphingomyelinase 2 (nSMase2) [28]; (2) miRNA motif and sumoylated heterogeneous nuclear ribonucleoproteins

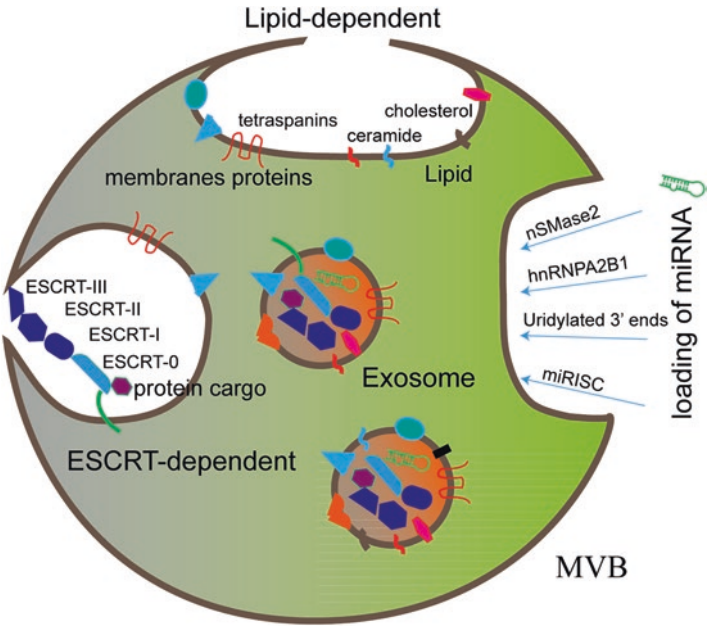

Fig. 18.3 Mechanism of sorting proteins, lipids and miRNAs into exosomes. Most ubiquitinated proteins are sorted into exosomes in ESCRT-depedent pathway. The membranes proteins and most lipids are sorted into exosomes via the lipid dependent way. The sorting of miRNAs involves lipid, nSMase-2; protein, hnRNPA2B1, miRSIC. In addition, the miRNAs with uridylated 3′ ends are mostly sorted into exosomes

(hnRNPs)-dependent pathway. It has been shown that the certain GGAG motif in the miRNA sequences can be recognized by the sumoylated hnRNPA2B1 [29]. The complex can be recognized by ESCRT-0 and subsequently recruited to the endosomal membranes; (3) The 3′-end of the miRNA sequence-dependent pathway. The 3′ end of the miRNA sequence contains critical signals that direct miRNA sorting into either exosomes or cells cytoplasm depending on whether the 3′ ends are uridylated or adenylated [30]; (4) The miRISC complex is formed between by mature miRNAs and assembly proteins and this complex is enriched in exosome.

3.3 Exosome Release

Once specific molecules are sorted into intraluminal endosomal vesicles, MVBs move and subsequently fuse to the plasma membrane. Several Rab proteins, a subfamily of small GTPases, are involved in regulating the transport of MVBs. Once MVBs have reached the plasma membrane, target SNARE (t-SNARE, Soluble Nethylmaleimide sensitive fusion protein attachment protein receptor in target cell) and VAMP (v-SNAREs such as VAMP7 and VAMP2) proteins in vesicle participate

in the fusion of MVB to the plasma membrane and subsequent release of MVBs to the outside of the cells. Various lipids and lipid-related enzymes regulate the secretion of these exosomes. The release of exosomes can be constitutive or induced by stimuli such as calcium, mitogens, cytokines or exercise [31].

3.4 The Effect of Stress on Biogenesis and Release of Exosomes

It is also known that many different types of cells can secret more than one type of exosomes. For example, breast cancer cells secrete several types of exosomes that differ in size and miRNA composition [32]. B-cell lymphoma [33] and colon carcinoma cells [34] were shown to release different subpopulations of exosomes which can be identified based on their surface antigens. In addition, exosome composition is affected by cellular state. Exosome content can be altered by exposing cells to hypoxia, starvation, oxidative stress or other cellular insult. It was shown that the number of exosomes containing miR-210 was increased when cells were cultured in hypoxia chamber [35]. Exosomes biogenesis and release are also influenced by pH. Sphingomyelin and ganglioside GM3 are enriched in exosomes derived from cells grown under acidic microenvironments [36]. The proteins involved in apoptosis, cell proliferation and tumor invasion are altered within exosomes when cells were exposed to irradiation [37] and anti-tumor drugs [38]. Membrane-associated proteins of exosomes released from human macrophages were altered after mycobacterium tuberculosis infection. Mesenchymal stem cells (MSCs) and cardiac progenitor cells release exosomes containing angiogenenic factors under ischemic environment [39, 40].

3.5 Exosome Uptake by Target Cells

It was shown that circulating exosomes increased immediately after marathon and declined to prerace levels 24 h after the race [41]. These findings suggest that exercise promotes exosomes uptake by target cells.

As depicted in Fig.18.4, exosome can enter the cells through the interaction between ligand-receptor or fusion to cell membranes. The fusion process is regulated by phosphatidylserine on exosome membrane. Exosomes can also be taken up by endocytic pathways, such as clathrin-dependent endocytosis, or by clathrin-independent pathways such as caveolin-mediated uptake. It appeared that a heterogeneous population of exosomes may enter into cells via different routes, which are depend on proteins and lipid on the surface of both the vesicle and the target cell [42].

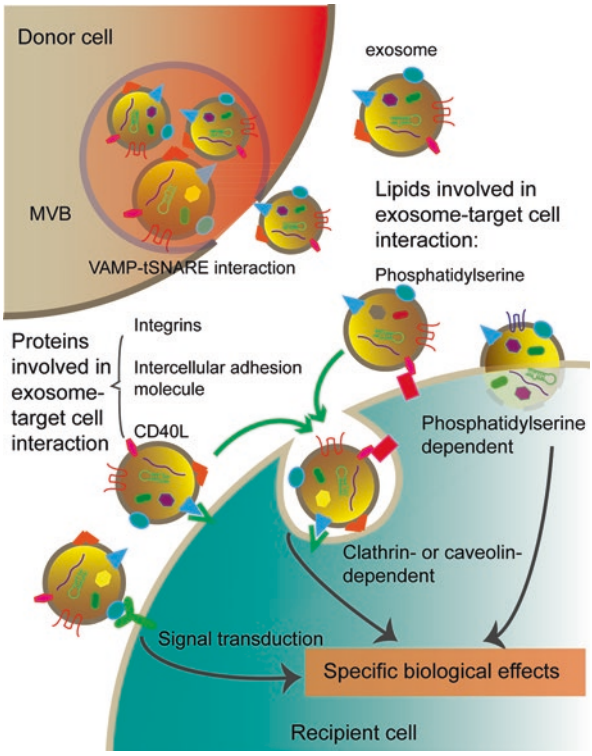

Fig. 18.4 Interaction between exosome and target cells. Donor cells release exosomes into extracellular matrix or circulation. These exosomes enter target cells through molecular interacting with recipient cells. A variety of exosomal molecules, such as integrins, intercellular adhesion molecule-1, CD40L and phosphatidylserine are involved in the interaction between exosomes and targets cells

Several molecules are involved in the interaction between exosomes and target cells. It is known that proteins are required for exosomes uptake because exosome uptake can be inhibited by proteinase K treatments. These proteins are glycoproteins with mannose- and sialic acid-glycosylation modifications [43]. Clinical data demonstrated that exosomal integrins can be used to predict organ specific metastasis. For example, exosomal integrins α6β4 and α6β1 are associated with lung metastasis [44]. Interactions through integrins have also been reported in exosomes from other cell types including endothelial cells, smooth muscle cells, and leukocytes. Intercellular adhesion molecule-1 located in exosomes derived from atherosclerotic human plaques can integrate into endothelial cells. Exosomes expressing glycoprotein-Ib interact with neutrophil integrin (Mac-1) in neutrophil, leading to neutrophil activation [45]. $CD40L^+$ located in exosomes can interact with endothelial CD40 and promotes angiogenesis, which may increase plaque vulnerability in atherosclerotic lesions [46]. Sonic Hedgehog located in exosomes from T-cells stimulates target Patched/Smoothened receptors to induce angiogenesis [47]. With in vivo cellular stretch, exosomes released by cardiomyocytes are enriched in angiotensin II type-1 receptors (AT1Rs) and administration of AT1R-enriched exosomes can restore blood pressure responsiveness to angiotensin II in AT1R-KO mice [48]. HSP70 located on the exosome surface can bind to toll-like receptor-4 on the cardiomyocyte surface, leading to activation of pro-survival pathways in cardiomyocytes.

In addition, integrins and immunoglobulins [49], proteoglycans [50] and lectin [51] are also involved in the exosome uptake by target cells.

Lipids, such as phosphatidylserine, are key determinants of the interaction between membrane vesicles with target cells. It was shown that phosphatidylserine microparticles can bind to CD36 scavenger receptor in platelet [52], leading to ADP-dependent platelet activation and promotes thrombosis in mice. The phosphatidylserine-moiety located on endothelial microparticles can interact with endothelial phosphatidylserine receptor to prevent apoptosis of endothelial cells [53].

As mentioned above, exosome composition, release and uptake are influenced by extracellular stress. We assume that exercise may also induce changes in the molecular composition of exosomes. We envision a future when exosomes can be modified to improve its interaction with recipient cells. For example, exosomes containing HSP70 can be used to treat cardiovascular diseases.

3.6 Exosome Isolation, Purification and Identification

The most commonly used methods for exosome purification include differential centrifugation, high-speed ultracentrifugation, size-exclusion chromatography, ultrafiltration, and commercial kits such as ExoQuick™ and Total Exosome Isolation™ [54]. Using the colorectal cancer cell line LIM1863 as a cell model, Greening et al. evaluated different exosome isolation methods including ultracentrifugation (UC-Exos), density based separation (DG-Exos), and immunoaffinity capture using anti-EpCAM (CD326)-coated magnetic beads (IAC-Exos). Based on electron microscopy examination for exoxomes diameter, and immunoblotting for exosome markers (Alix, TSG101, HSP70), they concluded that IAC-Exos was the most effective method to isolate exosomes, while density-based separation (DG-Exos) provides significant advantages when the immunoaffinity is not possible due to the lack of suitable antibodies [55]. Exosome also be analyzed by tandem-mass-spectrometry for high-resolution lipidomic and proteomic analyses and high-throughput sequencing of RNA.

4 The Exosomes Induced by Exercise in Cardiovascular Diseases

Exosome has been recognized as an important paracrine factor to improve myocardial function after acute myocardial infarction [56]. Once anchored to the target cells, and exosomes release miRNA and HSP to protect heart from ischemia induced damage.

4.1 Exosome Effect on Cardiovascular Diseases

Ischemic heart diseases result from loss of functional cardiomyocytes and eventually develop into heart failure. Over the past 15 years, transplantation of stem cell, such as the skeletal muscle myoblast [57], haematopoietic stem cells [58, 59], mesenchymal stem cells (MSCs) and cardiac progenitor cells (CPCs) [60] has been shown to improve heart function and the beneficial effects were mostly due to paracrine effects [56]. The paracrine factors were originally thought to be growth factors or cytokines, but recently, exosomes were also included in the list [22]. Injection of exosomes derived from cardiosphere [61], cardiac progenitor cell [62], cardiac stem cell [63], embryonic stem cell [64], mesenchymal stem cell [40] and induced pluripotent stem cells [10] in infarcted hearts has shown beneficial effects similar to injection of their respective stem cells. On the other hand, the beneficial effects exerted by stem cells disappeared when exosome excretion was blocked. Compared to stem cells, exosome appear to be less immunogenic although it also express histocompatibility antigens; In addition, exosome-based approaches are more convenient to use, although repeated injections of exosomes might be needed to achieve a sustainable effect [63].

It was shown that exosomes protect injured myocardium mainly through the release of protein and RNA molecules (Table 18.1), especially microRNA. For example, HSP70 and HSP90 released by exosomes derived from rat cardiomyocytes have cytoprotective effects. $CD34^+$ stem cell-derived exosomes contain high level of pro-angiogenic factor sonic hedgehog (SHH), which stimulated tube formation of endothelial cells cultured on Matrigel, and promoted angiogenesis in vivo and restored cardiac function in a mouse model of acute myocardial infarction (AMI) [65, 66]. Exosomes derived from mouse MSCs contain miR-22 which has anti-apoptotic effect on cardiomyocytes through downregulation of methyl-CpG binding protein 2 [67]. Exosomes from rat neonatal MSC over-expressing GATA-4 contain miR-19a, which activate Akt through downregulation of phosphatase and tensin homolog (PTEN) [11]. Administration of exosomes isolated from human cardiac progenitor cells (CPCs) improved cardiac function by inhibiting apoptosis and stimulating angiogenesis in a rat model of AMI. Interestingly, miR-146a can partially mimick the beneficial effects of CPC-derived exosomes on cardiac function [68, 69]. ESC-derived exosomes enriched with miR-294 from mouse promote neovascularization and cardiomyocyte survival in a mouse model of AMI [64]. In addition, miR-214 is required for endothelial cell to secrete exosomes that promote angiogenesis [70].

Exosomes can also produce unwanted effects. For example, exosomes released from cardiac fibroblasts contained high levels of miR-21-3p/miR-21, which stimulates angiotensin II production and its receptor expression in cardiomyocytes, leading to cardiomyocyte hypertrophy [71, 72]. In an LPS-induced model of sepsis, platelet derived exosomes induced apoptosis in endothelial cells [73]. Exosomes enriched in miR-320 inhibits endothelial cell proliferation and migration in diabetic rats [74]. So, exosomes can be either helpful or harmful for our health depending on where they come from and what kinds of cargo they carry.

Table 18.1 The effect of exosomes on cardiovascular system

Exosomes source	Functional molecules	Effects	Recipient	References
Beneficial effects				
CM	HSP70, HSP90	Prosurvival	CM	[79]
CD34+ stem cells	Sonic hedgehog (SHH)	Angiogenesis	EC	[65, 66]
MSCs	miR-22, miR-19a	Anti-apoptosis	CM	[67]
CPCs	miR-210,132,146a-3p	Anti-apoptosis, promote angiogenesis	CM, EC	[68, 69]
ESC	miR-294	Promote neovascularization, CM survival, CPCs proliferation	EC, CM, CPCs	[64]
EC	miR-214	Migration, angiogenesis	EC	[70]
Pathogenic effects				
EC	ICAM-1	Vascular inflammation	EC	[80]
CM in cardiac pressure overload	Angiotensin II R1	CM hypertrophy	CM, EC, VSMC	[71]
EC	MiR-146-a	Inhibits angiogenesis	CM	[81]
Cardiac fibroblasts	miR-21-3p/miR-21,	CM hypertrophy	CM	[71, 72]
Platelet in LPS-sepsis		EC apoptosis and CM inflammation	EC, CM	[73]
Circulating	miR-320	Inhibits proliferation and migration	EC	[74]
Diagnosis marker		**Predicting disease**		
Circulating	miR-144 precursor in circulating exosomes and miR-144 in myocardium	Coronary remote ischemic preconditioning		[75]
Circulating	p53-responsive miRs (miR-192, miR-194, miR-34a)	Heart failure induced by AMI		[76]
Circulating	miR-126, miR-199a	Stable coronary artery disease		[77]
Circulating	miR-519e-5p	Early phase of acute myocardial infarction (AMI)		[82]
Circulating	miR-133a	AMI and severity of coronary lesions in CHD		[78]

CM Cardiomyocytes; *EC* Endothelial cell; *VSMC* vascular smooth muscle cell; *PPCM* peripartum cardiomyopathy; *ICAM-1* intercellular adhesion molecule-1

Table 18.2 The change and biological effects of miRNA responsed to exercise

miRNA	Exercise and object	Biological effects	References
miR-1, miR-133a, miR-499-5p, miR-208a, miR-126, miR-146a	Marathon/ healthy male runners	Skeletal and cardiac muscle damage, and systemic inflammation	[41]
c-miRNAs (miR-19b, miR-148a, miR-221, miR-223, miR-320a, miR-361, and miR-486)	Grazing /cattles	Physiological adaptation	[84]
miR-1, miR-21, miR-27a/b, miR-29a/c, miR-30e, miR-99b, miR-100, miR-124, miR-126, miR-133a/b, miR-143, miR-144, miR-145, miR-208a, miR-222	Swimming aerobic exercise	Promotes angiogenesis, inhibits cardiac fibrosis	[85]
miR-214, miR-1	Exercise training / individual of myocardial infarction	Exercise can restore both microRNA levels and improve cardiac function	[86]

In some cases, the molecules in the exosome can be used as biomarker. For example, remote ischemic preconditioning (RIPC) could improve cardiac function and systemic release of miR 144 plays an important role in the cardioprotection induced by RIPC [75]. In patients with AMI, p53-responsive miRs (miR-192, miR-194, miR-34a) carried by exosomes are associated with development of heart failure [76]. In patients with stable coronary artery disease, the expression of miR-126 and miR-199a in circulating exosomes can predict the occurrence of cardiovascular diseases [77]. Circulating miR-133a level correlates with the severity of coronary lesions in patients with AMI [78].

4.2 The Function of Exosomal miRNA Induced by Exercise in Cardiovascular Diseases

MicroRNAs are a class of 17–24 nt small, noncoding RNAs [83], which regulate the expression of genes by binding to the 3′-untranslated region (3′-UTR) of target mRNAs. The miRNAs secreted into the blood were called “circulating miRNAs” (c-miRNAs). Most of c-miRNAs are transported with exosomes to protect itself from being degraded by the RNase in bloodstream. Recently, it had been shown that exercise can influence miRNAs expression in exosomes (Table 18.2), leading to specific biological effects.

C-miRNAs enriched in muscle (miR-1, miR-133a, miR-499-5p), cardiac tissue (miR-208a), the vascular endothelium (miR-126), and inflammation related miR-146a in healthy male marathon runners were increased immediately after the mara-

thon and declined to initial levels or lower 24 h after race completion. It has been shown previously that marathon can induce skeletal and cardiac muscle damage and inflammation [41]. Compared to housed cattles, grazing cattles have lower levels of miR-19b, miR-148a, miR-221, miR-223, miR-320a, miR-361, and miR-486 [84]. Thus, c-miRNAs can be used as the biomarker of exercise.

Interestingly, different miRNAs are regulated by different types of exercise. For example, swimming regulates miRNA-1, -21, -27a/b, -29a/c, -30e, -99b, -100, -124, -126, -133a/b, -143, -144, -145, -208a, and -222; and running regulate miRNA-1, -26, -27a, -133, -143, -150, and -222. All of these miRNAs promote beneficial physiological left ventricular remodeling through regulating their target genes [85]. Intracellular Ca^{2+} handling is often impaired after MI due to altered expression of NCX (sodium/calcium exchanger 1) and Serca-2a (sarcoplasmic reticulum Ca^{+2} ATPase-2a) in cardiomyocytes. NCX and Serca2a are targeted by miR-1 and miR-214, respectively. It was shown that the levels of microRNA-1 was reduced, while miR-214 was increased after infarction. However, these changes were normalized in animals subjected to exercise [86]. Indeed, exercise can restore intracellular Ca^{2+} handling, Ca^{2+} sensitivity, and contractile function in animal models of myocardial infarction [87].

In summary, moderate aerobic exercise alter the level and composition of miRNAs in the circulating exosomes, which produces cardioprotective effects after MI. More work is needed to understand what miRNAs are altered and how these changes affect the outcome of patients with myocardial infarction.

4.3 The Function of HSP Induced by Exercise in Exosome in Cardiovascular Diseases

Heat shock proteins (HSPs) are a group of proteins that are produced by cells in response to a wide variety of stressful conditions, which include heat, UV light, hypoxia and exercise [88]. HSPs are found in virtually all living organisms and plays an important role in maintaining cellular homeostasis by helping to stabilize and refold proteins that are damaged by stress [89]. HSPs have been classified according to their molecular weight. The focus of the current review is on the inducible HSP72, HSP60 and HSP20.

Previous studies showed that exercise can induce cardioprotection, which is correlated with elevated cardiac HSP70 levels when rats were exposed to ischemia and reperfusion (I/R) injury [90, 91]. Enhanced expression of intracardial or circulating HSP 70/72 during exercise is dependent on temperature environment [92–94], gender [93, 95] and age [96, 97]. Exercise in a warm environment increases the myocardial HSP 70/72 mRNA level, whereas the HSP70/72 level was unchanged in cold environment [92, 94, 98, 99]. The increase of HSP72 was more obvious in men than women after exercise [95]. HSP70 decreases with age in a normal population [96] in response to exercise. It is known that acute exercise can increase HSP72 in the peripheral circulation [100]. It was shown that HSP72 is released into the human

Table 18.3 Exercise type known to induce various HSPs in cardiovascular system

Exercise type	Species	Final training time	HSP member	Tissues examined	References
Treadmill	Rat	3–5 days	HSP 72	Heart by western-blot	[92]
Treadmill	Human	60 min 70% of peak oxygen consumption	HSP 72	Blood by ELISA	[100]
Half-marathon	Human	Under competition condition	HSP70, HSP60, HSP70	Peripheral leukocytes by flow cytometry and RT-PCR	[104, 105]
Semirecumbent cycle ergometer	Human	120 min	HSP72	Blood by ELISA	[106]
Treadmill	Rat	60 min	HSP20	Heart by western-blot	[107]
Cycling	Human	30 min	HSP27	Blood by ELISA	[108]
Handgrip exercise	Human	2,5,10,20,22,25,30, 50 min	HSP27	Blood by ELISA	[109]

circulation by exosomes [101]. The heart consists of myocardium, endocardium and epicardium, which communicate to each other in order to maintain normal cardiac function. Recent studies suggest that HSPs might be one of the proteins that are involved in cellular communication. Several studies revealed that HSP20 regulates myocardial angiogenesis and cardiac function. It was shown that diabetic cardiomyocytes could release harmful exosomes, which contain lower levels of HSP20 than normal ones. However, harmful exosomes could become protective by raising HSP20 levels in cardiomyocytes [102]. Blockade of exosome generation by GW4869 could reduce HSP20-mediated cardioprotection in diabetic mice [102], suggesting that cardiomyocyte – derived HSP20 was transported by exosomes. Furthermore, it was shown that HSP20-induced cardioprotection may be mediated at least in part by promoting angiogenesis [103]. Gupta showed that exosomes also mediated the release of HSP60 from cardiomyocytes [79]. Exercise induce changes of HSPs in cardiovascular system are summarized in Table 18.3.

5 Perspectives and Challenges

Emerging research suggests that exercise is one of the most effective methods to provide cardioprotective effects with little cost. However, too much exercise may be harmful to our health. It was shown that long-distance running may cause damage in cardiac muscle, induce inflammation [41], and increase the risk of cardiovascular

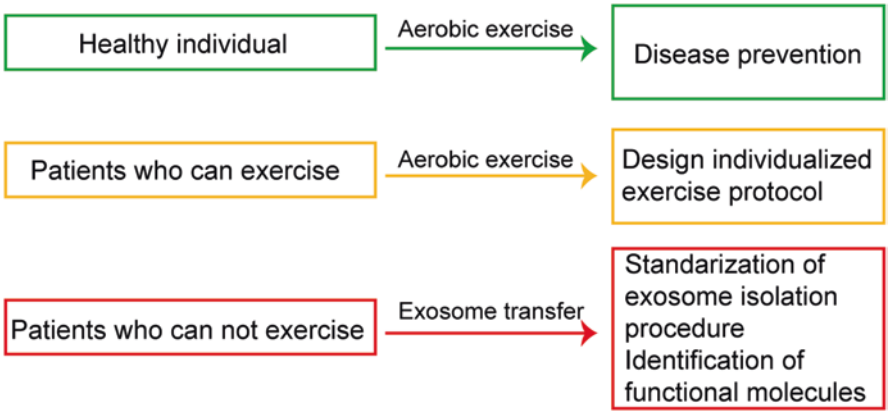

Fig. 18.5 The perspectives and challenges for using exercise induced exosomes as potential therapy. Moderate-intensity aerobic exercise can prevent the development of cardiovascular diseases and provide therapeutic benefit for people who already have the disease. For patients who can not tolerate exercise, the option would be to inject exosomes from healthy young people after exercise or to inject synthetic exosomes containing necessary beneficial molecules

events [110]. Therefore, further research will be needed to determine how much exercise is best for each clinical condition. The American Heart Association recommend at least 30 min moderate-intensity aerobic activity at least 5 days per week for a total of 150 min each week [111]. However, patients who suffer from heart failure and other chronic diseases have limited capacity for exercise. Potential therapeutic options for these patients include injection of exosomes from young healthy people after moderate-intensity exercise. Alternatively, synthetic exosomes carrying desired molecules can be given to patients who are not able to do exercise. Obviously, we must identify what kinds of molecules are released after exercise and to dissect out the beneficial molecules from the ones that are detrimental (Fig. 18.4).

Although moderate-intensity exercise offers significant health benefit, the molecules that mediate the beneficial effect remain to be explored (Fig. 18.5). It is now clear that some of the beneficial molecules are carried by exosome released during exercise. The next step toward the development of therapeutic strategy would be to understand how exercise affects the biogenesis, release and uptake of exosomes and how much exercise is needed to produce enough exosomes to treat a particular condition. As we are moving forward toward exosome based therapy, we should also identify the nature of the molecules carried by the exosomes and understand why and how certain molecules are specifically selected and sorted into the exosomes. We should also keep in mind that exosomes may carry undesired molecules that could be harmful and the question is how do we prevent these harmful molecules from being sorted to the exosomes. Once these tasks have been accomplished, we can then design synthetic exosome for patients who cannot tolerate regular exercise. Another question that needs to be answered is how exosomes reach their target cells. One possibility is that exosomes are only taken up by diseased tissue and cells. If so, the interaction between exosomes and target cells should be specific.

Understanding how exosomes recognize their recipient cells would be a huge leap toward targeted therapy for not only cardiovascular diseases but also for cancer and neurodegenerative diseases. Finally, standard protocols for isolation and characterization of exosomes should be developed in order to compare studies from different investigators and to ensure therapeutic efficacy and reproducibility.

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Part III
Exercise Dosing and Prescription

Chapter 19
Exercise Dosing and Prescription-Playing It Safe: Dangers and Prescription

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Abstract Cardiac rehabilitation is a comprehensive and multidisciplinary program, and exercise training is extremely crucial in the whole program. In the past decades, many researches have shown the beneficial effects of exercise for cardiovascular disease (CVD) is indisputable Nevertheless, only a well-designed exercise prescription may achieve the ideal benefits. In this chapter, we will have a discussion of what is exercise prescription and how to establish a scientific and appropriate exercise prescription for CVD patients depending on the current scientific evidence and recommendations.

Keywords Exercise • Cardiac • CVD • Prescription

1 An Brief Introduction to the Principles of Exercise Prescription

Exercise prescription (Ex R_x) commonly refers to the specific plan of fitness-related activities that are designed for a specified purpose, which is often developed by a fitness or rehabilitation specialist for the client or patient. Table 19.1 is the comparison of the similarities and differences between drug prescription and exercise prescription.

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Table 19.1 Drug and exercise prescription

Drug prescription		Exercise prescription	
Drug	ibuprofen	**Types**	Walking
Dosage	600 mg	**Intensity**	Moderate
Method	taken orally	**Time**	20 min/day
Frequency	TID (three times a day)	**Frequency**	5 times/week
Precautions	immediately stop taking if any gastrointestinal discomfort presents	**Volume**	At least 5400 steps/day
Duration	7 days	**Progression**	Gradually increase walking time or speed
		Other information	Continue through life-time

The principles of exercise prescription used to have four aspects, known as FITT(frequency, intensity, time and type), but in the recent few years, American College of Sports Medicine (ACSM) recommendations [1] prefer FITT-VP rather than FITT. V and P represent volume and progression respectively. Compared to FITT, FITT-VP can do a better job in providing exercise prescription ensuring that each prescription is detailed enough to be performed by each individual.

An exercise training program should be individualized rather than standard, and ideally is designed to meet individual health and physical fitness goals, including their social participation and daily activities to maximize the outcomes.

Exercise Frequency

Exercise frequency can be understood as the number of days per week dedicated to an exercise program, and it is an important contributor to health/fitness benefits that result from exercise.

Exercise Intensity

Exercise intensity refers to how much energy is expended when performing an activity.

Measurement Methods of Exercise Intensity (Table 19.2)

(1) HRR* method: Target HR (THR) = [(HR_{max} − HR_{rest}) × % intensity desired] + HR_{rest}

(2) VO_2R* method: Target $V O_2R = [(VO_{2max} - VO_{2rest}) \times \%\,\text{intensity desired}] + VO_{2rest}$

(3) HR method: Target HR = HR_{max} × % intensity desired

However, for some patients, HR is not a valid indicator of exercise intensity due to the pathology or medications [2, 3]. For examples, individuals having the adrenergic blocking agent (i.e., β-blocker) might have a more attenuated HR response to exercise compared to individuals who didn't take this medication. Also these patients would have an increased or decreased maximal exercise capacity because of the medication. Thus other responses, such as BP, oxygen saturation, or subjective parameters such as rating of perceived exertion (PRE), symptoms of dizziness/light-headedness or breathlessness, could be utilized instead.

Table 19.2 ACSM Recommendations for exercise intensity

Cardiorespiratory endurance exercise					Resistance exercise
Intensity	%HRR or %VO_2R	%HR_{max}	% VO_{2max}	MET	RPE Borg scale (rating on 6–20 scale)
Very light	<30	<57	<37	<2.0	Very light: ≤9
Light	30–< 40	57–< 65	37–< 46	2.0–< 3.0	Very light to fairly light: 9–11
Moderate	40–< 60	64–< 76	46–< 64	3.0–< 6.0	Fairly light to somewhat hard: 12–13
Vigorous	60–< 90	76–< 96	64–< 91	6.9–< 8.8	Somewhat hard to very hard: 14–17
Near maximal to maximal	≥90	≥96	≥91	≥8.8	≥Very hard: ≥18

(4) VO_2 method: Target $VO_2 = VO_{2max} \times$ % intensity desired
(5) MET method: Target MET = [VO_{2max}/3.5 mL/$_{(kg \bullet min)}$] × % intensity desired
(6) Rating of Perceived Exertion (PRE) method

*HRR: heart rate reserve,
VO_2R: oxygen uptake/consumption reserve

Exercise Time
Exercise time/duration is prescribed as a measure of the amount of time physical activity is performed (i.e., time session/day, and per week).

Exercise Type
Based on the current researches on exercise prescription, aerobic exercise, muscular fitness (resistance training), flexibility exercise and neuromotor are the good choices of exercise types to improve and/or maintain health. For each of these four types, there are a number of specific related exercises. In the following content, we will have a more detailed elaboration of each exercise type.

Exercise Volume
Exercise volume is the product of Frequency, Intensity, and Time (duration) of exercise. Evidence supports the important role of exercise volume in realizing health/fitness outcomes. Thus, exercise volume may be used to estimate the gross energy expenditure of an individual's Exercise prescription. MET-min/week and kcal/week can be used to estimate exercise volume in a standardized manner. MET-min and kcal/min can then be used to calculate MET-min/week and kcal/week that is accumulated as part of an exercise program to evaluate whether the exercise volume is within the ranges that will likely result in health/fitness benefits.

Exercise Progression
The progression of exercise or the rate of progression in an exercise program varies depending on the individual's health status, physical fitness, training responses, and exercise program goals. Therefore, there is no absolute recommended value. However, there is some recommended steps. Firstly, progression may include the increase of any of the components of the FITT principle according to the

individual's tolerance. During the initial phase of the exercise training program, increasing exercise time/duration (i.e., min/session) is recommended. Any progression in the FITT-VP principle of exercise prescription should be made gradually to avoid large increases in any of the FITT-VP components and thus minimize risks of muscular soreness, injury, undue fatigue, and the long-term risk of overtraining. Following any adjustments in the exercise prescription, the individual should be monitored for any adverse effects of the increased volume, such as excessive shortness of breath, fatigue, and muscle soreness, and downward adjustments should be made if individuals can't tolerate the exercise [1].

2 Scientific Establishment and Implementation of Exercise Prescription

Some severe accidents occur in clients or patients with excessive exercise which would stimulate body's stress response, leading to the hyperexcitability of sympathetic nerves and excessive secretion of hormones like catecholamine, as well as increased HR and BP in a short time. In some severe cases, excessive exercise may induce angina or other acute cardiovascular events which would do great harm to the controlling of CHD. Therefore, exercise prescription should be safe and effective for any client or patient (Table 19.3).

What is safety? When having cardiac exercise training to achieve the improvement of CVD, it should avoid any cardiovascular events (i.e., angina attack, sudden death, etc.), metabolic dysfunction or musculoskeletal problems (i.e., bone, joint and ligaments) caused from improper exercise type or intensity. If individuals can attain their goals of exercise training, such as achieving higher cardiopulmonary capacity, greater muscle strength and mass, losing weight, etc., the exercise will be effective.

To attain these two characteristics of safety and effectiveness, our establishment and implementation are required to be scientific. The scientificity of exercise prescription is based on the rudimentary knowledge of clinical medicine, sports medicine, rehabilitation and health science.

2.1 Pre-participation

Before establishment of exercise prescription, it is important to evaluate whether the individual is suitable and safe for exercise. So the Physical Activity Readiness Questionnaire (PAR-Q) and the modified AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire are commonly used for self-guidance in health screening.

Individuals should let professionals to review the completed PAR-Q or AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire to determine if they need to have the risk assessment for CVD risk. The risk classification are as follows:

Table 19.3 Principles and elements of exercise prescription

		Pre-participation	Establishment	Implementation	
		Scientificity			
		Individualization		program components	Exercise guidance and supervision
Purpose	**Safety**	Health screening; Risk assessment; Exercise testing Appropriate and effective FITT-VP parameters are based on the exercise testing results	Parameters of FITT-VP depending on: (1) Objective factors: 1) Individual's goals; 2) Individual's interests and hobbies. (2) Subjective factors: 1) Individual's health condition and exercise capacity; 2) Individual's social environment, like jobs; 3) Individual's economic capacity.	Warm-up, conditioning, cool-down and stretching	Individuals and clinical practitioners
	Effectiveness				

1. low risks: asymptomatic, <2 risk factors;
2. moderate risk: asymptomatic, ≥2 risk factors;
3. high risk: symptomatic, or known cardiovascular, pulmonary, renal, or metabolic disease.

Individuals with high risks are highly recommended for exercise testing before exercise. However, the information gathered from exercise testing for individuals with low to moderate risks would be useful in establishing a safe and effective exercise prescription. Common exercise testing includes maximal exercise testing, submaximal exercise testing and symptom limited exercise testing (ECG exercise testing and cardiopulmonary exercise testing).

For patients with CVD, cardiac exercise training would be much more violent than their daily activities in life. Therefore, they are strongly advised to consult physician or professional sports medicine physicians to determine whether they need to have ECG exercise testing before exercise depending on screening their HR, BP, physical fitness, medication and complications. If they are not safe for exercise testing, we can use the non-exercise testing findings to determine their risk stratification which is critical for establishing individualized exercise prescription for CVD patients as well. Risk stratification criteria from the AACVPR are presented in Table 19.4.

Table 19.4 American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) risk stratification criteria for patients with cardiovascular disease

		Characteristics	Non-exercise testing findings
Lowest risk	Characteristics of patients at lowest risk for exercise participation (all characteristics listed must be present for patients to remain at lowest risk)	(1) Absence of complex ventricular dysrhythmias during exercise testing and recovery	(1) Resting ejection fraction ≥50%
		(2) Absence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness, during exercise testing and recovery)	(2) Uncomplicated myocardial infarction or revascularization procedure
		(3) Presence of normal hemodynamics during exercise testing and recovery (i.e., appropriate increases and decreases in heart rate and systolic blood pressure with increasing workloads and recovery)	(3) Absence of complicated ventricular dysrhythmias at rest
		(4) Functional capacity ≥7 metabolic equivalents (METs)	(4) Absence of congestive heart failure
			(5) Absence of signs or symptoms of postevent/ postprocedure ischemia
			(6) Absence of clinical depression

(continued)

Table 19.4 (continued)

		Characteristics	Non-exercise testing findings
Moderate risk	Characteristics of patients at moderate risk for exercise participation (any one or combination of these findings places a patient at moderate risk)	(1) Presence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness occurring only at high levels of exertion [≥7 METs])	Rest ejection fraction 40% to 49%
		(2) Mild to moderate level of silent ischemia during exercise testing or recovery (ST-segment depression <2 mm from baseline)	
		(3) Functional capacity <5 MET	
Highest risk	Characteristics of patients at high risk for exercise participation (any one or combination of these findings places a patient at high risk)	(1) Presence of complex ventricular dysrhythmias during exercise testing or recovery	(1) Rest ejection fraction <40%
		(2) Presence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness at low levels of exertion [<5 METs] or during recovery)	(2) History of cardiac arrest or sudden death
		(3) High level of silent ischemia (ST-segment depression ≥2 mm from baseline) during exercise testing or recover	(3) Complex dysrhythmias at rest
		(4) Presence of abnormal hemodynamics with exercise testing (i.e., chronotropic incompetence or flat or decreasing systolic BP with increasing workloads) or recovery (i.e., severe post-exercise hypotension)	(4) Complicated myocardial infarction or revascularization procedure
			(5) Presence of congestive heart failure
			(6) Presence of signs or symptoms of post-event/ post-procedure ischemia
			(7) Presence of clinical depression

2.2 Establishment of Exercise Prescription

As elaborated in the table above, there are objective and subjective factors of establishing a safe and effective exercise prescription. For objective factors, individual's own goal plays a crucial role in the whole exercise training and motivates the individual internally. Also, when choosing exercise type, patients are encouraged to find some exercises which are more sustainable for them, and discuss with PTs to determine whether this type of exercise is suitable for the individual so that patients can achieve a more effective outcome.

The detailed FITT-VP parameters will be discussed in the following contents.

2.3 Implementation of Exercise Prescription

To minimize risks of muscle soreness, injury, fatigue, any long-term risk of overtraining or adverse cardiac events during exercise, we should pay attention to some common phases of exercise training. Noticing that exercise program is not only exercise itself, but also includes warm-up, cool-down, stretching exercises, and gradual progression of volume and intensity [1]. By performing these phases correctly, CVD patients can have a sustaining good exercise performance and achieve a better exercise outcome.

A single exercise training program should include the following phases:

1. Warm-up.
2. Conditioning and/or sports-related exercise.
3. Cool-down.
4. Stretching/flexibility.

Warm-up is a transitional phase that allows body to adjust to the changing physiologic, biomechanical, and bioenergetic demands from resting to exercise. Warm-up phase consists of at least 5–10 min of aerobic endurance and muscular fitness (resistance exercise) training with light-to-moderate intensity. Meanwhile, warm-up could improve the range of motion (ROM) and reduce the risks of injury during exercise as well [1] .

Conditioning phase includes all types of exercise, such as aerobic, resistance, flexibility, neuromotor exercise, and/or sports activities.

Cool-down phase involves at least 5–10 min aerobic and muscular endurance activity of light-to-moderate intensity. The aim of cool-down is to allow for a gradual recovery of heart rate and blood pressure, as well as the removal of metabolic products from the muscles tissue in exercise conditioning phase.

Stretching can prevent and improve soft tissue tightness. There may be some misunderstanding that stretching is warm-up or cool-down, but it isn't. Stretching is distinct from the warm-up and cool-down, it can be performed following the warm-up or cool-down phase or following the application of hot packs or other modalities which can increase the temperature of soft tissue, since warming the muscles improves ROM and help with stretching [1] (Table 19.5).

Table 19.5 Common phases of exercise training program

Warm-up	A minimum of 5–10 min of cardiorespiratory and muscular endurance activities with light-to-moderate intensity
Conditioning	A minimum of 20–60 min of aerobic, resistance, neuromotor, and/or sports activities (if the individual can accumulate at least 20–60 min/day of daily aerobic exercise, exercise bouts of10 min will be acceptable)
Cool-down	A minimum of 5–10 min of cardiorespiratory and muscular endurance activities with light-to-moderate intensity
Stretching/flexibility	A minimum of 10 min of stretching exercise performed after warm-up or cool-down phase

Adapted from Refs. [1, 4]

In addition to the common phases of exercise training program, good implementation needs exercise guidance and supervision as well. At the beginning, individuals may not familiar to the movement and be nervous, so PTs should give them oral instructions, comfort them to let them relax, and tell individuals to exhale during exertion and inhale during relaxation with the purpose of avoiding holding breath and Valsalva maneuver. Also, since individuals would focus on the movements, PTs should pay close attention to their HR, ECG, PRE, respiratory rate and other signs and symptoms to prevent them from getting injury. If patients present HR and/or BP reduction or obvious feeling of fatigue during exercise training, and all symptoms can't be adjusted or reverted by patients themselves, PTs should decrease exercise intensity or stop exercise immediately. For some older individuals, preventing falling is of great significance. However, we should make sure that each individual has the awareness of supervision by themselves through BP, respiratory rate or RPE so that they can independently complete exercises in the future.

3 Aerobic (Cardiorespiratory Endurance) Exercise Prescription and Detailed Exercise Programs

This is part, we will have a deeper understanding of aerobic (cardiorespiratory endurance) exercise prescription. This is not only for cardiovascular patients, but also as the general recommendation for most adults. Indeed, the aerobic exercise prescription for cardiovascular patients is adapted from the general one varying with the health condition of each individual. By having a whole picture of the aerobic exercise, we will thoroughly command it and sufficiently apply it for the people in need. For patients with CVD, we will have a clearer thought of the different aerobic exercise prescriptions during their rehabilitation program.

3.1 Frequency of Exercise

The frequency of aerobic exercise is recommended as 3–5 day/week for most adults and it varies with the intensity of exercise [1, 4–7]. Improvements in cardiorespiratory fitness are attenuated with exercise frequency > 3 day/week and there could be a plateau in improvement with exercise frequency > 5 day/week. If the frequency of exercise is too high, like over 5 days per week, it may increase the risks for injuries to human body. Therefore, vigorous intensity of exercise is not recommended for most adults [1].

3.1.1 Modified for CVD Patients

The prevention and treatment for CHD patients depend on the regular and healthy life style, including decreasing calorie uptake (i.e., reduce 500 kcal in daily diet), and keeping regular daily exercise (i.e., 30-min aerobic exerciser training) and

consistent exercise. Studies showed that if the exercise interval is more than 3–4 days, the achieved exercise result and accumulated effect will decrease. Thus, exercise frequency is recommended about 3–5 times per week, detailed number varies depending on the exercise volume. If exercise volume is relatively large, exercise interval can be 1–2 days, but no more than 3 days; if the exercise volume is relatively small and patient can tolerate, ideally once daily will be acceptable. For instance, some individuals with low physical strength can achieve health/fitness benefits for performing aerobic exercise once or twice per week, but exercise with this frequency would have some impact on body weight, energy and endurance sometimes. For these patients, multiple short (1–10 min) daily exercise sessions may be prescribed. If the individual's physical strength is not that bad and can tolerate more, frequency lower than twice per week would bring very limited improvement on cardiopulmonary fitness.

3.2 Intensity of Exercise

Determination of the appropriate exercise intensity is based on the overload principle. Overload principle refers to that the exercise load must be above the training stimulus threshold which can elicit a training or conditioning response so that adaption can occur. Once the adaption to a given load has taken place, exercise intensity must be increased for individual to achieve further improvement. Recent studies have shown that the minimum threshold of intensity for benefit would vary depending on the individual's cardiorespiratory fitness level and other factors such as age, health status, physiologic differences, genetics, habitual physical activity, and social and psychological factors [8, 9]. Thus, it would be difficult to precisely define an exact or standard threshold to improve cardiorespiratory fitness.

Moderate intensity like 40–60% heart rate reserve or VO_2R and/or vigorous intensity of aerobic exercise like 60–90% heart rate reserve or VO_2R are commonly recommended for most adults. Light intensity like 30–40% heart rate reserve or VO_2R is recommended for individuals with deconditioned health status.

3.2.1 Modified for CVD Patients

The intensity of exercise directly influences the treatment effect for CHD patients, so different patients should have an individualized program. To ensure the safety and efficacy of exercise training, the intensity must be controlled within the identified effective range. As elaborated above, exercise intensity may be prescribed using one or more of the following methods: (1) Based on results from the baseline exercise test, 40–80% of exercise capacity using the HR reserve, oxygen uptake reserve, or peak oxygen uptake (VO_{2peak}) methods; (2) RPE of 11–16 on a scale of 6–20 [10]; (3) Exercise intensity should be prescribed at a HR below the ischemic threshold; for example,<10 beats, if such a threshold has been determined for the patient.

For detail, exercise with moderate intensity is suitable for CHD patients, approximately 40–80% of VO_{2max} which is equal to 50–70% HR_{max}. As for CHD patients with obesity, low intensity (approximately 40–50% VO_{2max} or 50–60% HR_{max}) is recommended as lower intensity is beneficial to the utilization and consumption of fat. Intensity over 80% VO_{2max} have certain risks, elderly CHD patients may have more complications, therefore intensity below 50% VO_{2max} is appropriate for the them.

3.3 Types (Mode) of Exercise

Rhythmic, aerobic exercises involving large muscle groups are recommended for improving cardiorespiratory fitness [1]. When selecting the specific exercise, PTs can use the principle of specificity of training when selecting the exercise types in the exercise prescription. Table 19.6 shows aerobic exercise training categorized by the intensity and skill demands. Exercises in Group 1, recommended for all adults, require less skills to perform, and the intensity can easily be modified to accommodate a wide range of physical fitness levels. Exercises in Group 2 are typically performed at a vigorous intensity and are recommended for individuals who are at least of average physical fitness and who have been doing some exercises on a regular basis. Exercises in Group 3 require skills to perform, and therefore are best for individuals who have reasonably developed motor skills and physical fitness to perform the exercises safely. Exercises in Group 4 are recreational sports that can improve physical fitness but are generally recommended as the ancillary physical activities in addition to conditioning physical activities. In this group physical activities are recommended only for individuals who possess adequate motor skills and physical fitness to perform the sport. However, if patients have any hobby in this group, PTs can modify the exercise to accommodate individuals with lower skill and physical fitness levels (Table 19.6).

Although this is a table for people with different physical fitness levels, we need to consider the physical fitness levels and their exercise capacity of all CVD patients before they got the diagnosis or occurrence of CVD. This is because physical fitness levels and exercise capacity determine patients' potential exercise capacity and interests of exercise types. These information will help us to establish proper exercise prescription for the individual patient, motivate patients to actively participate in the exercise training program, and finally optimize the exercise training outcomes.

3.3.1 Modified for CVD Patients

Aerobic exercise is the vital foundation for CVD patients by increasing aerobic capacity and quality of daily life. Among various exercises, those with low to moderate intensity are more suitable for CHD patients. With the purpose of promoting whole body physical fitness, the exercise prescription should include the upper and

Table 19.6 Modes of Aerobic Exercise to Improve Physical Fitness

Group	Exercise description	Recommended for	Examples
1	Endurance activities requiring minimal skills or physical fitness to perform	All adults	Walking, leisurely cycling, aqua-aerobics, slow dancing
2	Various intensity endurance activities requiring minimal skills	Adults who are habitually physical active and/or at least average physical fitness	Jogging, running, rowing, aerobics, spinning, elliptical exercise, stepping exercise, fast dancing
3	Endurance activities requiring skills to perform	Adults with acquired skill and/or at least average physical fitness levels	Swimming, cross-country skiing, skating
4	Recreational sports	Adults with a regular exercise program and at least average physical fitness	Racquet sports, basketeball, soccer, down-hill skiing, hiking

Adapted from ACSM's Guidelines for Exercise Testing and Prescription. 7th ed

lower extremities, multiple forms of aerobic activities; besides, exercise equipment should also be incorporated into the exercise program. In outpatients, exercises like walking, jogging, cycling, swimming and moderate aerobic gymnastics with all muscles involved (aerobics, Mulan boxing, Taichi, etc.) are commonly used. Equipment like arm ergometer, combination of upper or lower extremity (dual action) cycle ergometer, upright and recumbent cycle ergometer, recumbent stepper, rower, elliptical tainer, stair climber and treadmill could be chosen for assisting exercise. Additionally, depending on different interests and hobbies, patients can choose recreational ball games as well, such as gate ball, bowling, badminton, etc.

It should be highlighted that, to maximize the improvement of exercise capacity for CVD patients, the combination of aerobic exercise and resistance training is optimal rather than only aerobic exercise or resistance training.

3.4 Exercise Time (Duration)

To obtain the volumes of exercise recommended in the following discussion, it is suggested that most adults should exercise 30–60 min per day which is equal to 150 min per week of moderate intensity exercise, 20–60 min per day or 75 min per week of vigorous intensity exercise, or the combination of moderate and vigorous intensity exercise per day [1, 4]. In recent years, there are some researches about the effect of shorter exercise time on cardiopulmonary diseases. For example, less than 20 min of exercise per day can be beneficial, especially in sedentary individuals. The time/duration of this physical activity may be performed at least 10 min per session continuously (i.e., one session) or intermittently, and can be accumulated

over the course of a day in one or more sessions of physical activity. Exercise bouts of 10 min may attain favorable adaptations in very deconditioned individuals, but further studies are in need [1].

3.4.1 Modified for CVD Patients

Patients with CHD can start the exercise training with a short time around 5–10 min/time, and gradually elongate the durance depending on the body's accommodation of exercise training and patient's health status. There should be 5–10 min warm-up before exercise and at least 5-min relaxation after exercise. Moreover, time to target HR should be ensured over 10–30 min. For the interrelationship of exercise intensity and exercise time, exercise time should adjust with exercise intensity. When exercise intensity is relatively higher, exercise time should be shorter at the same time, and vice versa. For those younger patients with milder condition and better physical strength, they can perform the combination of more vigorous exercise intensity with shorter exercise time. In the opposite, for the elderly and obese patients, PTs can prescribe them with the combination of lower exercise intensity with longer exercise time.

3.5 Exercise Volume

The results of epidemiological studies and randomized clinical trials have shown there is a dose-response association between the volume of exercise and health/fitness outcomes (i.e.,the greater amount of physical activity, the greater increase of health/fitness benefits) [1, 11]. It is not clear whether there is a minimum or maximum amount of exercise needed to attain health/fitness benefits. However, a total energy expenditure of ≥500–1000 MET-min/week is consistently associated with lower rates of CVD and premature mortality. Thus, ≥500–1000 MET-min/week is a reasonable target volume for an exercise program for most adults [1]. This volume is approximately equal to

(a) 1000 kcal/week of moderate intensity, physical activity (or about 150 min/week);
(b) an exercise intensity of 3–5.9 METs (for individuals weighing between 68 and 91 kg);
(c) 10 MET-h/week [1].

It should be noted that low volumes of exercise (i.e., 4 $kcal/_{(kg \bullet week)}$ or 330 kcal/week) can result in health/fitness benefits in some individuals, especially in individuals who are deconditioned [1, 11]. Even lower volumes of exercise may also have benefits in health/fitness, but evidence is still insufficient to make definitive recommendations [1].

3.6 Progression

The general role of progression in aerobic exercise training are the same as the recommendation elaborated above. Initially, an increase in exercise time/duration per session of 5–10 min every 1–2 week over the first 4–6 week of an exercise training program is reasonable for the average adult [1]. After the individual has been exercising regularly for ≥1 month, the frequency, intensity and time of exercise are gradually adjusted upward over the next 4–8 month, or longer for older adults and very deconditioned individuals to meet the recommended quantity and quality of exercise (Table 19.7).

3.7 Examples of Detailed Aerobic Exercise Programs

1. Aerobic exercise prescription (endurance) with low intensity
   (1) exercise goals: to improve aerobic exercise capacity, decrease risks for CVD, decrease body weight and mass of body fat
   (2) exercise types: fitness walking or jogging
   (3) exercise intensity: low, moderate
   (4) target HR: 40–60% HR_{max}
   (5) RPE: <12 (mild)

Table 19.7 Aerobic (Cardiovascular Endurance) exercise evidence-based recommendations

FITT-VP	Evidence-based recommendation
Frequency	(1) ≥ 5 day/week of moderate exercise;
	(2) ≥ 3 day/week of vigorous exercise;
	(3) a combination of moderate and vigorous exercise on ≥3–5 day/week
Intensity	(1) Light-to-moderate intensity: deconditioned individuals;
	(2) Moderate and/or vigorous intensity: most adults
Time	(1) Exercise bouts of <10 min: very deconditioned individuals;
	(2) < 20 min/day: sedentary individuals;
	(3) 30–60 min/day of moderate exercise, or 20–60 min/day of vigorous exercise, or a combination of moderate and vigorous exercise per day: most adults
Type	Regular, purposeful exercise that involves major muscle groups and is continuous and rhythmic in nature
Volume	(1) ≥ 500–1000 MET min/week
	(2) Pedometer step counts: ≥7000 steps per day steps, can start with 2000 steps per day
Progression	A gradual progression of exercise volume by adjusting exercise duration, frequency, and/or intensity is reasonable until the desired exercise goal (maintenance) is attained.

Adapted from Ref. [1]

(6) 40–60% VO_{2max} or maximum power of exercise testing
(7) exercise time: 10–15 min
(8) exercise frequency: 3–4 times/week

2. Aerobic exercise prescription (endurance) with moderate intensity

(1) exercise goals: to improve aerobic exercise capacity, enhance respiratory capacity, decrease risks for CVD, decrease body weight and mass of body fat
(2) exercise types: fitness walking or jogging
(3) exercise intensity: moderate, high
(4) target HR: 60–70% HR_{max}
(5) RPE: 12–13 (moderate)
(6) 60–75% VO_{2max} or maximum power of exercise testing
(7) exercise time: 30 min
(8) exercise frequency: 4–5 times/week

3. High-intensity intermittent exercise training (HIIT) prescription

(1) exercise goals: to improve aerobic and anaerobic exercise capacity, decrease feeling of fatigue
(2) exercise types: ergometry or running at moderate velocity
(3) exercise intensity: high
(4) target HR: 75–90% HR_{max}
(5) RPE: 14–16 (vigorous)
(6) 75–90% VO_{2max} or maximum power of exercise testing
(7) exercise time: 2–5 min, 3–6 sets with interval of 1–2 min, interval can be rest or mild exercise with decreased intensity (20–30% HR_{max})
(8) exercise frequency: 4–5 times/week

4. Super high-intensity intermittent exercise training prescription

(1) exercise goals: re-establish and coordinate skeletal muscle function, decrease feeling of fatigue
(2) exercise types: ergometry or treadmill
(3) exercise intensity: high
(4) target HR: 90–95% HR_{max}
(5) RPE: 14–16 (vigorous)
(6) 90–95% VO_{2max} or maximum power of exercise testing
(7) high-intensity intermittent: 5 circles 30/90 s rhythm (30 s load, 90 s rest); rotate velocity 80–100 r/min; intensity: maximum or nearly maximal power (from exercise assessment); recovery time: 10 min; power: 0–25 w; rotate velocity: 60 r/min
(8) exercise frequency: 3–5 times/week

4 Muscular Fitness Exercise Prescription and Detailed Exercise Programs

Lots of researchers have shown the benefits of muscular fitness on muscle strength, endurance, and power. Also, higher levels of muscular strength are linked with lower risk of all-cause mortality, fewer CVD events, lower risk of developing physical function limitations, and lower risk for nonfatal disease [1]. In addition to increasing muscle strength, improvements in body composition, blood glucose levels, insulin sensitivity, and BP in individuals are also expected [12, 13].

Moreover, a number of researches have shown the clinical benefits for:

(a) treating metabolic syndromes, including diabetes, obesity, hypertension and dyslipidemia;
(b) increasing bone mass so that preventing or reversing osteoporosis;
(c) reducing musculoskeletal disorder [14];
(d) reducing risks for accidental falls in the elder [15, 16];
(e) decreasing pain and disability [1, 17];
(f) helping with improving depression and anxiety, increasing vigor, and reducing fatigue [1];
(g) improving exercise performance and activities of daily life, particularly in older individuals.

4.1 Frequency of Resistance Exercise

It is recommended by ACSM to have the frequency of resistance exercise 4 days per week as long as each muscle group is trained for 2–3 days per week. This means all muscle groups don't need to be trained in one day. For examples, upper extremity resistance exercises can be arranged on Mondays and Thursdays, and lower extremity resistance exercises can be arranged on Tuesdays and Fridays. Through flexible arrangement, individuals will be more likely to adhere to exercise so that they can attain a better exercise outcome. Of course, individuals can train all muscle groups in one day, but the repetition for each muscle group should be reduced consequently to make sure muscles are not over trained and thus prevent musculoskeletal injuries.

4.1.1 Modified for CVD Patients

The frequency will be the same as for most adults. In addition, resistance training should be performed after the aerobic component of the exercise session to allow for adequate warm-up.

4.2 Types of Resistance Exercise

According to the muscle contraction types, resistance exercise can be classified as isometric exercise, isotonic exercise and isokinetic exercise.

Also, resistance training can use body weight or equipments such as elastic bands, cuff and hand weights, wall pulleys and machines. Resistance training includes (1) Single-joint exercise refers to exercise which targets one major muscle groups. Some common single-joint exercises are biceps curls, triceps extensions, quadriceps extensions, leg curls (for hamstrings), and calf raises; (2) Multi-joint exercise is also called compound exercises which affects more than one muscle group, such as press-ups, pull-down, dips, lower back extension, abdominal crunch, squats, etc.

It should be noticed that the trainings for agonists and antagonists are important for muscles balance. Some PTs are lack of the overall consideration of making exercises for clients or patients. When they completed the assessment, they may only focus on strengthening the weak muscles which may not help clients to attain the optimal exercise performance and may cause new problems.

4.3 Volume of Resistance Exercise (Repetitions and Sets)

In the aim of improving muscle strength, it is recommended for most adults that the repetitions per set is 8–12. However, since there is a reversed relationship between the intensity of resistance exercises and the number of repetitions, 8–12 repetitions approximately equals to 60–80% 1-RM. When the intensity of exercises increases, the repetitions should relatively decrease. ACSM recommends that each set should be performed until muscle fatigues but not muscle failure because exerting muscles to failure increases the likelihood of injury or debilitates residual muscle soreness, particularly among novices [18].

To attain the ideal volume, exercise sets are important as well. ACSM recommendation shows that each muscle group should be trained for a total of two to four sets. Individuals can choose different exercises in these sets, but should train the same muscle group. Compared to the same exercise types, various exercises with the same target training muscle may prevent individuals from long-term mental 'staleness' and may improve adherence to the training program. Although for most adults, the recommended volume is 2–4 sets per muscle group, but for some novices, a single set per muscle group can significantly improve muscular strength as well [1, 18]. Moreover, a reasonable rest interval between sets is 2–3 min.

If the individual's aim is to improve muscular endurance, they can adopt a higher number of repetitions, probably around 15–25, with shorter rest intervals and fewer sets such as 1 or 2 sets per muscle group [1, 18]. The according intensity is lower which should be no more than 50% 1-RM.

4.3.1 Modified for CVD Patients

Patients with CVD who are older or relatively deconditioned should begin with a relative small exercise volume with low resistance intensity and more repetitions.

4.4 Progression and Maintenance

If the purpose of an individual is to keep progression of his/her muscle strength, he/she needs greater stimuli after muscles' adaptation to the current resistance exercise due to the 'progressive overload' principle. The common approaches of progression are (1) increasing the resistance; (2) increasing the sets per muscle group; (3) increasing the frequency. However, initially we will choose to increase the amount of resistance. The increase of resistance intensity can not be too much, and the individual needs to complete the repetitions at the intensity without significant muscle fatigue and difficulty in completing the last repetition of that set. Then we can gradually increase sets or exercise frequency for each muscle group accordingly.

If the individual has attained the desired levels of muscular strength and mass, and now he/she just wants to maintain that levels, it is not necessary to progressively increase the training stimulus. Thus, he/she only needs to perform the muscle fitness training one day per week with the regular parameters of exercise as he/she used to choose before.

4.4.1 For CVD Patients

The general principle of progression in muscle fitness training for CVD patients are the same as the one for most adults. But we need to make sure that the patient has adapted to the current intensity by using the intensity measurements indicators like HR, BP, PRE, etc. and closely pay attention to patient's response to the increased intensity (Table 19.8).

4.5 Examples of Detailed Resistance Exercise Programs

With the present of decreased muscle strength, we can use resistance exercise to strengthen the weaken muscles. Usually, we will establish Ex Rx according to each patient's general health status and each muscle group's function. CVD patients are commended to choose proper load. Exercise training program should consist of 8–10 items each time, for 15–20 min with 1–2 min rest between every two exercises.

Some examples of detailed Ex Rx for muscle fitness are as follows:

Table 19.8 Resistance exercise evidence-based recommendations

FITT-VP		Exercise-based recommendation
Frequency		2–3 days/week for each big muscle group with a rest of ≥48 h between sessions
Intensity		(1) 20–50% 1-RM: for older individuals to improve power
		(2) 40–50% 1-RM (very light-to-light intensity): for sedentary individuals beginning a resistance training and for older individuals beginning exercise to improve strength
		(3) ≥ 50% 1-RM (light-to-moderate intensity): improve muscular endurance
		(4) 60%–70% 1-RM (moderate-to-vigorous intensity): for novice to intermediate exercisers to improve strength
		(5) ≥ 80% 1-RM (vigorous-to-very vigorous intensity): for experienced strength trainers to improve strength
Time		The optimal one is unknown, but with 2–3 min rest intervals between each set of repetitions
Type		(1)Resistance exercises involving each major muscle group are recommended.
		(2)Multi-joint exercises affecting more than one muscle group and targeting agonist and antagonist muscle groups are recommended for all adults.
		(3) Single joint exercises targeting major muscle groups may also be included in a resistance training program, typically after performing multi-joint exercise(s) for that particular muscle group.
		(4) A variety of exercise equipment and/or body weight can be used to perform these exercises.
Volume	**Repetitions**	(1) 8–12 repetitions: improve strength and power in most adults
		(2) 10–15 repetitions: improve strength in middle-aged and older individuals starting exercise
		(3) 15–20 repetitions: improve muscular endurance
	Sets	(1) A single set: older and novice exercisers
		(2) 2–4 sets: improve strength and power for most adults
Progression		Greater resistance intensity, and/or more repetitions per set, and/or higher frequency

Adapted from Ref. [1]

1. Biceps flexion and extension resistance exercise

   (1) exercise goals: increase upper-limb muscle strength, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
   (2) movement description: standing upright with arms naturally drooping, holding dumbbells with proper weight (<40% 1RM), gradually and slowly flexing elbow to 90°then slowly putting down; repeat the movements as described above.
   (3) exercise intensity: 10–15 times*1 set
   (4) exercise time: 2 min
   (5) exercise frequency: 2 times/week

2. Knee flexion resistance exercise in prone

   (1) exercise goals: increase lower-limb muscle strength, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
   (2) movement description: prone, choosing Thera-band with proper load (<40% 1RM), fixing one side on the bed and fixing the other side on the ankle, gradually and evenly flexing knee to 90° then slowly putting down; repeat the movements as described above.
   (3) exercise intensity: 10–15 times*1 set
   (4) exercise time: 2 min
   (5) exercise frequency: 2 times/week

3. Upper abdominal muscle resistance exercise

   (1) exercise goals: increase upper abdominal muscle strength, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
   (2) movement description: supine, choosing dumbbells with proper weight (<40% 1RM), raising and holding the dumbbells overhead, gradually and evenly crunching upper body till 30°to the bed, then slowly putting down; repeat the movements as described above.
   (3) exercise intensity: 10–15 times*1 set
   (4) exercise time: 2 min
   (5) exercise frequency: 2 times/week

4. Gastrocnemius muscle resistance exercise

   (1) exercise goals: strengthen the posterior calf muscles, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
   (2) movement description: long-sitting, choosing Thera-band with proper load (<40% 1RM), holding one side on the hands and fixing the other side on the feet, gradually and evenly doing plantarflexion, then slowly returning feet to the original position; repeat the movements as described above.
   (3) exercise intensity: 10–15 times*1 set
   (4) exercise time: 2 min
   (5) exercise frequency: 2 times/week

5. Bridge Endurance Exercise

   (1) exercise goals: strengthen the back muscles, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
   (2) movement description: supine, flexing both knees at 90°, elevating hips and extending, holding the position for several seconds depending on the patient's capacity, so does the height of hip. Then gradually and slowly returning the hip to bed. If the patient can tolerate more loads, PTs can choose sandbag with proper weight. Repeat the movements as described above.

(3) exercise intensity: 30–50 times*1 set
(4) exercise time: 3 min
(5) exercise frequency: 2 times/week

6. Ergometry Cycling

(1) exercise goals: strengthen the lower-limb muscles, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
(2) movement description: sitting with upper body straight up, holding handrail well and riding the ergometry with steady velocity. Load varies according to the individual's capacity by adjusting the resistance of ergometry.
(3) exercise intensity: HR 90–100 bmp/min
(4) exercise time: 10 min
(5) exercise frequency: 2 times/week

7. Squat

(1) exercise goals: strengthen the lower limbs muscles, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
(2) movement description: standing against the wall with upper body straight up, gradually squatting to a proper angle and slowly standing up. Repeat the movements as described above. Add loads as needed.
(3) exercise intensity: 30–50 times*1 set
(4) exercise time: 3 min
(5) exercise frequency: 2 times/week

8. Push-ups on Wall in Standing

(1) exercise goals: strengthen the upper-limb muscles, prevent decreased muscle strength or muscle atrophy induced from reduced daily activities, decrease risks for CVD and improve quality of life
(2) movement description: standing towards the wall with upper body straight up. Putting hands against at the level of shoulder, gradually and evenly flexing elbows and returning to the original position; repeat the movements as described above. Adjusting the movement with steady objects with different height.
(3) exercise intensity: 30–50 times*1 set
(4) exercise time: 3 min
(5) exercise frequency: 2 times/week

5 Flexibility Exercise (Stretching) and Detailed Exercise Programs

Flexibility exercise can improve joint range of motion (ROM) or flexibility [7]. The purpose of flexibility training is to improve decreased ROM or maintain the normal joint ROM to have sufficient exercise. It is recommended to perform flexibility

exercise training after muscle temperature is increased through active warm-up or through some passive modalities like hot packs, warm whirlpool, etc.

Common types of flexibility exercise are included in the Tables 19.9 and 19.10. Ballistic stretching or 'bouncing' stretching should be noticed only suitable for adults who often participate in activities involving ballistic movements such as basketball. Proprioceptive neuromuscular facilitation (PNF) techniques typically involve an isometric contraction followed by a static stretch in the same muscle/tendon group, which is superior to dynamic or slow movement stretching in improving joint ROM, but requires a partner to help with the stretching.

Table 19.9 Flexibility exercise definitions

Ballistic methods/"bouncing" stretches	Use the momentum of the moving body segment to produce the stretch [19]
Dynamic or slow movement stretching	Involves a gradual transition from one body position to another, and a progressive increase in reach and ROM as the movement is repeated several times [20]
Static stretching	Involves slowly stretching a muscle/tendon group and holding the position for a period of time (i.e., 10–30 s). Static stretches can be active or passive [21]
Active static stretching	Involves holding the stretched position using the strength of the agonist muscle as movements common in many forms of yoga [1].
Passive static stretching	Involves assuming a position while holding a limb or other part of the body with or without the assistance of a partner or device (such as elastic bands or a ballet barre) [1].
Proprioceptive neuromuscular facilitation (PNF)	Methods typically involve an isometric contraction of the selected muscle group followed by a static stretching of the same group [22, 23].

Adapted from Ref. [1]

Table 19.10 Flexibility exercise evidence-based recommendations

FITT-VP	Evidence-based recommendation
Frequency	(1) 2–4 times repetition of each flexibility exercise (2) ≥ 2–3 days/week, ideally perform everyday
Intensity	Stretch to the point of feeling tightness or slight discomfort
Time	(1) Adults:Static stretch for 10–30 s; (2) The elder:Static stretch for 30–60 s; (3) PNF stretching: 3–6 s light-to-moderate contraction (e.g., 20–75% of maximum voluntary contraction) followed by a 10–30 s assisted stretch
Type	Static flexibility (active or passive), dynamic flexibility, ballistic flexibility, and PNF
Volume	60 s of total stretching time for each flexibility exercise
Progression	Optimal progression methods are unknown.

Adapted from Ref. [1]

The joint ROM can be improved immediately after performing flexibility exercise and can have a gradualimprovement after approximate 3–4 week of stretching with minimum 2–3 times/week. Some researchers pointed that regular flexibility exercise training may reduce musculotendinous injuries, prevent low back pain, or delay the onset of muscle soreness, but more evidences are needed.

Long-time stretching exercises or repetitive quick stretching could cause an immediate, short-term decrease in muscle strength, power, and sports performance. Therefore, if muscle strength and muscle power are very important to certain exercise, stretching before exercise may have a negative effect on the performance [24].

Detailed examples of flexibility exercise prescriptions are as follows:

1. Shoulder
   (1) exercise goals: maintain or improve the flexibility of shoulder, prevent muscle strain in daily activities
   (2) movement description: standing, bending forward and putting hands on a fixed object with certain height, pressing shoulder down.
   (3) exercise intensity: (30s-60s) * (2–3) sets
   (4) exercise time: 5 min
   (5) exercise frequency: 3–4 times/week
2. Lumbar region
   (1) exercise goals: maintain or improve the flexibility of lumbar spine, prevent muscle strain in daily activities
   (2) movement description: starting from hands and knees, rocking backwards, and bringing buttock towards heels. Pausing for a moment and then rocking forward and allowing abdomen to sag towards the floor. Holding 5–10s for each position.
   (3) exercise intensity: (30s-60s) * (2–3) sets
   (4) exercise time: 5 min
   (5) exercise frequency: 3–4 times/week
3. Lower extremity
   (1) exercise goals: maintain or improve the flexibility of lower extremity, and prevent muscle strain in daily activities
   (2) movement description: Lying on back and gently holding one leg behind the knee. Slowly extending the lower leg until a gentle stretch is felt in the back of the thigh. Patient can dosiflex their foot, bring toes towards head to enhance the stretch. Holding 5–10s for each position.
   (3) exercise intensity: (30s-60s) * (2–3) sets
   (4) exercise time: 5 min
   (5) exercise frequency: 3–4 times/week

6 Neuromotor Exercise

For older adults at risk of falls, neuromotor exercise helps to maintain and improve balance and motor skills (balance, agility, coordination and gait) [1, 7, 25]. This includes multifaceted activities such as tai chi, yoga, and recreational activities using paddles or sport balls (i.e., table tennis and badminton) to challenge hand-eye coordination. Sometimes neuromotor exercise is also called functional fitness training. The optimal types of neuromotor exercise, doses (i.e., FIT), and training regimens are not known for adults of any age. Studies demonstrated a recommended protocol which has implemented the neuromotor exercise 2–3 days/week with 20–30 min for each session for 60 min per week.

A summary of the FITT-VP principle of Exercise prescription for neuromotor exercise is listed in Table 19.11.

7 Exercise Prescription for Heart Disease

Patients with the history of cardiac artery disease would have the potential for development of atherosclerosis at the later stage in their life time. Also, patients with cardiac histories commonly have physical therapy treatments at other stages throughout their lives. For instance, patients with the previous MI might require ambulation training as a result of a fractured hip. Therefore, it is prudent for PTs to understand the pathophysiology of cardiac condition and the energy demands being placed on the patients to adjust the exercise prescription accordingly.

First of all, to make sure the safety and outcomes, we need to know the indications and contraindications for exercise.

Indications

- Medically stable post–myocardial infarction (MI)
- Stable angina

Table 19.11 Neuromotor exercise evidence-based recommendations

FITT-VP	Evidence-based recommendation
Frequency	≥2–3 days/week
Intensity	The optimal volume is not known. Depending on individual's health condition, exercise capacity and exercise goals
Time	≥20–30 min/day
Type	Exercises involving motor skills (e.g., balance, agility, coordination, gait), proprioceptive exercise training, and multifaceted activities (e.g., tai chi, yoga)
Volume	The optimal volume is not known.
Progression	Methods for optimal progression are not known, but PTs can use some motor control theories as the reference.

Adapted from Ref. [1]

- Coronary artery bypass graft (CABG) surgery
- Percutaneous transluminal coronary angioplasty (PTCA)
- Stable heart failure caused by either systolic or diastolic dysfunction (cardiomyopathy)
- Heart transplantation
- Valvular heart surgery
- Peripheral arterial disease (PAD)
- At risk for coronary artery disease (CAD) with diagnoses of diabetes mellitus, dyslipidemia, hypertension, or obesity
- Other patients who may benefit from structured exercise and/or patient education based on physician referral and consensus of the rehabilitation team

Contraindications

- Unstable angina
- Uncontrolled hypertension — that is, resting systolic blood pressure (SBP) >180 mm Hg and/or resting diastolic BP (DBP) >110 mm Hg
- Orthostatic BP drop of >20 mm Hg with symptoms
- Significant aortic stenosis (aortic valve area > 1.0 cm^2)
- Uncontrolled atrial or ventricular arrhythmias
- Uncontrolled sinus tachycardia >120 beats/min)
- Uncompensated heart failure
- Third-degree atrioventricular (AV) block without pacemaker
- Active pericarditis or myocarditis
- Recent embolism
- Acute thrombophlebitis
- Acute systemic illness or fever
- Uncontrolled diabetes mellitus
- Severe orthopedic conditions that would prohibit exercise
- Other metabolic conditions, such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia (until adequately treated)

7.1 Inpatient and Outpatient Exercise Program

Patients with certain coronary artery diseases (CAD) which need percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG), cardiac valve replacement or myocardial infarction (MI) should receive a sound cardiac rehabilitation program, consisting of assessment, exercise and education. This cardiac rehabilitation program begins in the hospital and extends into maintenance phase. The inpatient phase refers to Phase I, outpatients' phases are Phase II (the exercise-training period) and the maintenance period as Phase III.

Inpatient/Phase I: Formal physical activity begins until no more angina, no increase of cardiac troponin level, no compensatory symptoms for new heart failure

(i.e dyspnea with moist rales at rest), no new or significant arrhythmia or ECG changes, resting heart rate 50–100 bpm, resting blood pressure 90–150/60–100 mmHg, blood oxygen saturation > 95% after 8 h since patients hospitalized.

Outpatients/Phase II &Phase III often start in the first 3 weeks after discharge. Routine pre-exercise assessment of risk for exercise should be performed before, during, and after each rehabilitation session, including: (1) HR; (2) BP; (3) Body weight (weekly); (4) Symptoms or evidence of change in clinical status not necessarily related to activity (e.g., dyspnea at rest, lightheadedness or dizziness, palpitations or irregular pulse, chest discomfort); (5) Symptoms and evidence of exercise intolerance; (6) Change in medications and adherence to the prescribed medication regimen; (7) Consideration of ECG surveillance that may consist of telemetry or hardwire monitoring, "quick-look" monitoring using defibrillator paddles, or periodic rhythm strips depending on the risk status of the patient and the need for accurate rhythm detection.

Table 19.12 shows the detailed exercise goals and prescription for inpatient and outpatient programs respectively.

It should be highlighted that, outpatients are encouraged to perform some of above exercise sessions independently. Independently completing some exercise will optimize the exercise benefits and improve their ADLs in the future.

7.2 Congestive Heart Failure

Exercise training for patients with heart failure has been shown to improve functional capacity, symptoms, and quality of life [26]. The standard recommendations for exercise training for heart failure are similar to those for patients with known CVD, as defined earlier in this chapter.

In addition to the common exercise training, patients with heart failure need ventilator muscle training in particular aspatients with heart failure are known to have poor ventilatory muscle strength [27]. Breathing exercises [28, 29] and inspiratory muscle training [30, 31] have been consistently shown to have benefits in patients with heart failure who may have dyspnea and use accessory muscles to help breathing. Diaphragmatic breathing may help reduce excessive use in accessory muscle and reduce the work of breathing. Pursed-lip breathing is commonly used in promoting the positive end-expiratory pressure in patients with COPD. In fact it can also help slow down the respiratory rate in patients with CHF (congestive heart failure) [29, 32].

Meanwhile, strength of the ventilator muscles can be enhanced through the use of a device like a threshold inspiratory muscle trainer. To achieve the improvements in the maximal inspiratory pressure, patient breathes with this device which provides resists during inspiration to strengthen the inspiratory muscles. A general recommended protocol is to use 20% of the maximal inspiratory pressure 3 times per day for 5–15 min at each session.

Table 19.12 Goals and prescription for cardio-inpatient and outpatient programs

	Inpatients		Outpatients
Goals	(1) Identify patients with significant cardiovascular, physical, or cognitive impairments that may influence the performance of physical activity.		(1) Develop and assist the patient to implement a safe and effective formal exercise and lifestyle physical activity program.
	(2) Offset the deleterious physiologic and psychological effects of bed rest.		(2) Provide appropriate supervision and monitoring to detect change in clinical status.
	(3) Provide additional medical surveillance of patients and their responses to physical activity.		(3) Provide ongoing surveillance data to the patient's health care providers in order to enhance medical management.
	(4) Evaluate and begin to enable patients to safely return to activities of daily living (ADL) within the limits imposed by their CVD.		(4) Return the patient to vocational and recreational activities or modify these activities based on the patient's clinical status.
	(5) Prepare the patient and support system at home or in a transitional setting to optimize recovery following hospital discharge.		(5) Provide patient and spouse/partner/family with education to optimize secondary prevention (e.g., risk factor modification) through aggressive lifestyle management and judicious use of cardioprotective medications.
	(6) Facilitate physician's referral and patient's entry into an outpatient cardiac rehabilitation program.		
Exercise prescription	**Frequency**	Mobilization: Two to four times per day for the first 3 days of the hospital stay.	At least 3 days but preferably on most days of the week. For patients with very limited exercise capacities, multiple short (1–10 min) daily sessions may be prescribed.
	Intensity	Seated or standing resting heart rate (HRrest) +20 beats/min for patients with an MI and +30 beats/min for patients recovering from heart surgery; with an upper limit ≤120 beats/min that corresponds to an RPE ≤13 on a scale of 6–20.	(1) 40%–80% of exercise capacity using the HR reserve (HRR), oxygen uptake reserve (VO_2R), or peak oxygen uptake (VO_{2peak}) methods
			(2) RPE of 11–16 on a scale of 6–20
			(3) Exercise intensity should be prescribed at a HR below the ischemic threshold.
	Time	Begin with intermittent walking bouts 3–5 min as tolerated with exercise bouts of progressively increased duration. The rest period may be a slower walk (or complete rest at the patient's discretion) which is shorter than the duration of the exercise bout. Attempt to achieve a 2:1 exercise/rest ratio.	Warm-up and cool-down activities for 5–10 min. 20–60 min aerobic exercise per session. After a cardiac-related event, patients may begin with as little as 5–10 min of aerobic conditioning with a gradual increase in aerobic exercise time of 1–5 min per session or an increase in time per session of 10%–20% per week.
	Type	Walking	Combination of aerobic exercise and muscle fitness exercise.

7.3 Special Considerations

7.3.1 Patients with a Sternotomy

To gain access to the heart, median sternotomy is usually performed as part of CABG and valve replacement surgery. The healing of sternal bone to an adequate stability is usually achieved by 8 weeks [33]. Patients with diabetes mellitus, obesity, immunosuppressive therapy, advanced age, and osteoporosis are relatively vulnerable to have complications such as infection, nonunion, and instability [34].

Clinical practitioners must be cautious in establishing exercise prescription for patients with a sternotomy, particularly within the first 8–12 week following the procedure with the following precautions:

1. Do not lift more than 8 pounds (4–8 weeks-check with surgeon)
2. Do not push or pull with arms when moving in bed or transferring (including wheelchairs)
3. Do not weight bear with arms
4. No overhead activities
5. Do not flex shoulders >90°
6. Avoid twisting or deep bending
7. Avoid reaching across body
8. No breath holding
9. Brace chest during coughing/sneezing

7.3.2 Recent Pacemaker or Implantable Cardioverter Defibrillator Implantation

Cardiac pacemakers are used to restore an optimal HR and to synchronize atrial and ventricular filling and contraction in the setting of abnormal rhythms. Implantable cardiac defibrillators (ICDs) are devices that monitor heart rhythms and deliver shocks if life-threatening rhythms are detected. Exercise prescription considerations for those with pacemakers are as follows:

1. Programmed pacemaker modes, HR limits, and ICD rhythm detection algorithms should be obtained from the patient's cardiologist prior to exercise testing or training.
2. Exercise testing should be used to evaluate HR and rhythm responses prior to beginning an exercise program.
3. When an ICD is present, the HR_{peak} during the exercise test and exercise training program should be maintained at least 10 bpm below the programmed HR threshold for anti-tachycardia pacing and defibrillation.
4. After the first 24 h following the device implantation, mild upper extremity ROM activities can be performed and may be useful to avoid subsequent joint complications.

5. To maintain device and incision integrity, rigorous upper extremity activities such as swimming, bowling, lifting weights, elliptical machines, and golfing should be avoided for 3–4 week after implant. However, lower extremity activities are allowed.

7.3.3 Patients After Cardiac Transplantation

The Exercise prescription for patients with cardiac transplantation is different from other cardiac exercise prescriptions. In the first several months after surgery, the transplanted heart does not respond normally to sympathetic nervous stimulation. For instances, resting HR is elevated; the increase of HR during exercise is delayed and HR_{peak} is below normal. Hence, THR can't be used for measuring exercise intensity in exercise prescription for these patients. Optionally, RPE can be used to monitor the exercise intensity aiming from 11 to 16. In the exercise program, warm-up and cool-down should be relatively extended if the patient is limited by muscular deconditioning. Also stretching and ROM exercises are necessary. Research has shown that 1 year after surgery, approximately one-third of patients have a partially normal HR response to exercise and may be given a THR based on results from an exercise test (Squires).

Exercise training is of great significance for all individuals, especially for those individuals with CVD, such as coronary artery disease or congestive heart failure. Individuals with heart disease should recognize that a consistent exercise training program is a crucial part of the management of their disease and is as necessary as their medications. All members in the cardiac rehabilitation program are important for the recovery of patients with heart diseases. The role of the physiotherapist is to have a deep understanding of pathophysiology and exercise so that they can provide a safe and effective exercise prescription for all patients, and let them have a clear and sufficient understanding of the exercise prescription individualized for them.

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Erratum to: The Positive Effects of Exercise in Chemotherapy-Related Cardiomyopathy

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