Review

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Review

Exercise effects on left ventricular remodeling in patients with cardiometabolic risk factors

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Abstract: Left ventricular (LV) remodeling is a dynamic process which is characterized by abnormal LV wall thickness and altered myocardial geometry, and it is considered as a negative prognostic factor in both heart failure with reduced eject fraction (HFrEF) and heart failure with preserved eject fraction (HFpEF). Hypertension, type 2 diabetes (T2D) and obesity are strongly correlated with the development and the progression of LV remodeling, LV hypertrophy and LV systolic and/or diastolic dysfunction. Indeed, the beneficial impact of exercise training on primary and secondary prevention of cardiovascular disease (CVD) has been well-established. Recent studies highlight that exercise training enhances functional capacity, muscle strength and endurance, cardiac function and cardiac-related biomarkers, among patients with established coronary artery disease (CAD) or HF, thus improving substantially their cardiovascular prognosis, survival rates and needs for rehospitalization. Therefore, in this review article, we discuss the evidence of LV remodeling in patients with cardiometabolic risk factors, such as hypertension, T2D, obesity, and also highlight the current studies evaluating the effect of exercise training on LV remodeling in these patients.

Keywords: exercise; diabetes; obesity; hypertension; ventricular remodeling; heart failure

1. Introduction

It is estimated that more than 26 million adults suffer from heart failure (HF) worldwide, with the prevalence rates to grow rapidly [1]. According to current literature, 35-50% of patients with HF experience frequent rehospitalizations within 6 months of discharge, thus deteriorating their prognosis and incurring billions in costs [2]. Left ventricular hypertrophy (LVH) seems to be one of the leading cause of death worldwide and is characterized by increased left ventricular (LV) mass and cardiomyocyte hypertrophy [3]. Hypertension, type 2 diabetes (T2D), chronic kidney disease and aortic stenosis are considered major risk factors for LVH [4] [5]. Furthermore, LVH has been associated with increased risk for LV dysfunction, HF, arrythmias, stroke and sudden cardiac death [3].

LV remodeling is a dynamic process which is characterized by abnormal LV wall thickness and altered myocardial geometry, and it is considered as a negative prognostic factor in both heart failure with reduced eject fraction (HFrEF) and heart failure with preserved eject fraction (HFpEF). In more details, obesity and hypertension cause increase in systemic pressure, afterload and wall stress, thus leading to the development of LVH [6, 7]. Up to 60% of patients with hypertension may present with

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signs of increased LV mass on echocardiography [8]. Mild to moderate hypertension and LVH is commonly accompanied by varying degree of impaired LV diastolic filling with normal or mild increased systolic performance at rest, as well as diminished coronary vasodilator capacity [9]. Nevertheless, LVH might evolve to overt systolic and diastolic dysfunction, thus leading to the development and progression of HFrEF or HFpEF, respectively, as presented in *Figure 1*.

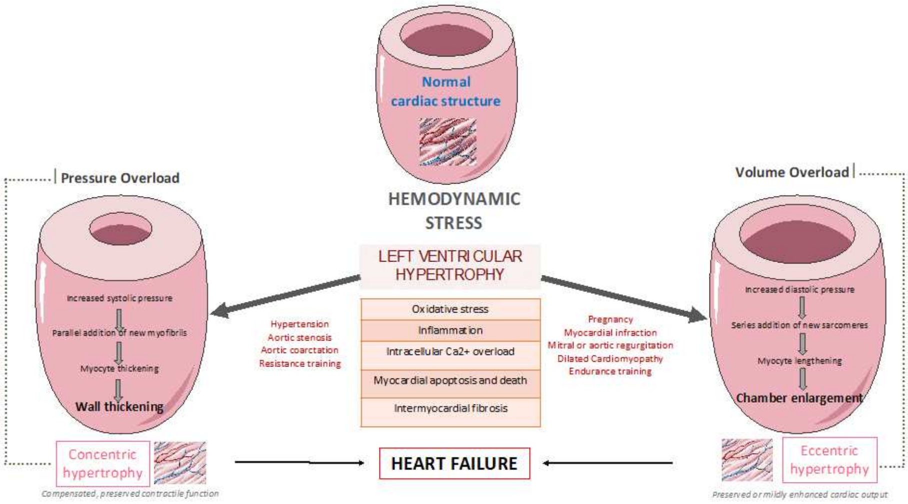

Figure 1. The pathway from left ventricular hypertrophy to heart failure.

Plenty complex and multifactorial mechanisms resulting in transcriptional, signaling, structural and electrophysiological changes are involved in this process of LV remodeling [10]. More specifically, oxidative stress and altered intracellular calcium metabolism provoke cardiomyocyte hypertrophy, thus resulting in impaired contraction and relaxation, as well as increased risk for fatal ventricular arrythmias and sudden cardiac death [11, 12]. Of note, interstitial and replacement fibrosis play a pivotal role in the progression of LV remodeling [8].

On the one hand, LVH regression seems to limit LVH-related adverse clinical outcomes and improve patient prognosis [13]. On the other hand, the beneficial impact of exercise training on primary and secondary prevention of plenty clinical conditions such as cardiovascular disease (CVD), T2D, as well as obesity has been well-established so far [14]. Recent studies highlight that exercise training enhances functional capacity, muscle strength and endurance, cardiac function and cardiac-related biomarkers, among patients with established coronary artery disease (CAD) [15] or HF [16], thus improving substantially their cardiovascular prognosis, survival rates and needs for rehospitalization [17].

In this review article, we discuss the evidence of LV remodelling among patients with cardiometabolic risk factors, such as hypertension, T2D, obesity and we also focus on current studies evaluating the effect of exercise training on LV remodeling in these patients.

2. LV remodelling pattern among patients with cardiometabolic risk factors

2.1. Athlete's heart

Exercise training typically increases heart rate and blood pressure, leading to specific cardiac changes among healthy individuals, especially the highly trained athletes[18]. This condition should be differentiated from hypertension-induced cardiac maladaptation and LVH, thus it is further discussed below. "Athlete's heart" is characterized by eccentric LVH, especially among elite athletes, and those participating in endurance and resistance training programs, whereas the related functional and structural changes occur parallel with exercise training, as an adaptation to intensive and chronic hemodynamic overload [19]. Therefore, LVH might be a physiological adaptation to strenuous physical exercise, as observed in athletes, whereas it is generally benign. However, it strongly correlated with the type of exercise [20]. Dynamic exercise, such as running and swimming, causes volume overload, whereas static exercise such a weightlifting, increases pressure load [19]. Aerobic exercise programs induce normally cardiac remodeling characterized by increased right ventricular (RV) and LV chamber dimensions and wall thickness, increased left atrial (LA) cavity size along with normal systolic and diastolic function, although resistance training increases mildly LV thickness, with no effect on LV chamber size [19]. The increase in LV wall thickness and LA cavity is even greater in master endurance athletes [21]. LV wall thickness may exceed the normal upper limits of 13 to 15 mm [22] up to 16mm in elite male athletes [23]. Of note, exercise programs combining both aerobic and anaerobic types of activities, such as prolonged cycling, rowing, and swimming result in mixed structural and functional cardiac adaptations and these athletes experience the most increase in LV mass [24].

Interestingly, it has been reported that athletes may have a 15-20% increase in LV wall thickness, a 10% increase in LV cavity size and a 24% increase in RV cavity size [25]. LV thickness up to 15mm is commonly apparent in most athletes, while the most thickened region is the anterior portion of the ventricular septum [26]. Morphologic adaptation to training in athletes enlarges the cavity size to an end-diastolic diameter ≥55 mm [6]. Nevertheless, "athlete's heart" differentiates from hypertension-induced cardiac maladaptation and LVH. The overall pattern of LVH in "athlete's heart" seems to be symmetric and homogenous [27]. However, athletes with LVH do not have impaired left ventricular ejection fraction (LVEF) or any evidence of systolic or diastolic dysfunction. Therefore, chronic exercise-mediated cardiac adaptations observed in athletes are considered to be normal hemodynamic responses, which do not correlate with increased risk of diastolic or systolic dysfunction, arrythmias, or adverse prognosis, whereas they regress gradually, when there is exercise restriction [28]. Moreover, cardiac dimensions, LV hypertrophy and LA dilatation generally regress to normal values after a period of detraining and deconditioning, which can take up to several years in longtime athletes [29]. However, an increase in LV mass, LV cavity size and LA diameter might be persistent up to 50% of endurance athletes even after 3 years of detraining [29].

2.2. Hypertensive heart disease

Chronic hemodynamic overload in hypertension provokes major structural and functional changes leading to LVH. In more details, chronically increase blood pressure cause LV pressure overload, thus increasing LV workload and resulting in LVH [6]. This clinical condition is characterized by hypertrophy of existing cardiomyocytes, addition of sarcomeres, increased deposition of collagen and extracellular matrix, leading to an increase in ventricular mass [30]. Typical echocardiographic structural findings, including concentric remodeling, concentric hypertrophy or even a combination of concentric and eccentric hypertrophy, along with increased LV wall thickness, LV diastolic and systolic dimensions, have been described. Functional changes cause activation of sympathetic and renin-angiotensin-aldosterone system, thus increasing myocardial wall stress and leading to detrimental systolic and diastolic dysfunction. At the later stages, impaired ventricular contractility and systolic HF may present [31]. Interestingly, healthy individuals, who do not exceed blood pressure levels above 150mmHg during exercise, do not stimulate cardiac remodeling, and as a result they are less likely to develop LVH [6]. So far, European Society of Hypertension along with European Society of Cardiology have announced recommendations for LVH evaluation based on electrocardiogram and echocardiogram findings. Although ECG is a low-cost and widely used method, echocardiogram is the most preferred method for assessing LV size and function [32].

2.3. Diabetic cardiomyopathy

T2D is a systemic disease with detrimental macro and micro-vascular complications. Patients with T2D have a 2.5-fold increased risk to develop HF, independently of age or concomitant comorbidities such as CAD and dyslipidemia [33, 34], whereas these patients represent the one third of HF population in clinical trials [35]. The term of "diabetic myocardiopathy" is a clinical condition characterized by impairments in cardiac structure and function independent of the macrovascular complications of diabetes (including hypertension, CAD and atherosclerosis) [36, 37]. Of note, cardiac

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dysfunction commonly remains clinically silent and as a result underdiagnosed until the latest stages of the disease, whereas almost 50% of asymptomatic, normotensive patients with T2D and good glycemic control demonstrate a degree of cardiac dysfunction [38].

Diabetes-induced LV diastolic dysfunction caused by prolonged and delayed LV filling and relaxation, often is presented in the absence of concomitant impairments in LV systolic function [39, 40]. Moreover, diabetes-induced abnormal collagen deposition, cardiomyocyte hypertrophy and cardiomyocyte loss via myocardial cell death pathways resulting in cardiac fibrosis and hypertrophy has been described in both animal and human studies [41–44]. Furthermore, coronary microvascular hypoperfusion as characterized by impairment in coronary flow reserve, and myocardial blood flow, with increased coronary resistance, have been also reported among patients with T2D [45]. Complex pathophysiological pathways including oxidative stress, inflammation, impaired $Ca2+$ metabolism, mitochondrial and metabolic dysfunction, endoplasmic reticulum stress, along with alterations to insulin sensitivity and signaling, gene regulation, neurohumoral activation and cardiac cell death seem to be the main contributors to the development and progress of diabetic cardiomyopathy [46, 47].

2.4. Obesity-related cardiomyopathy

Obesity is a multifactorial metabolic disorder characterized by a heterogeneous complex of biological, socioeconomic and environmental factors leading to adverse health outcomes [48, 49]. According to recent epidemiological data, it is estimated that more than 603 million adults suffer already from obesity worldwide, whereas prevalence rates grow rapidly [50]. Obesity has been strongly correlated with the presence of T2D, hypertension and various lipid disorders such as triglyceridemia, low levels of high-density lipoprotein, increased levels of small dense low lipoprotein and apoprotein B, thus increasing the cardiovascular risk [51, 52]. Especially, central, visceral obesity is a pivotal cardiovascular risk factor [53]. Pericardial and epicardial adipose tissue seem to be also a main contributor for CVD [54]. Obesity-induced insulin resistance, hyperinsulinemia, endothelial dysfunction, lipid accumulation, chronic low-grade systematic inflammation, oxidative stress and prothrombotic status seems to be the main pathophysiological pathways leading to the development and progression of CVD [54, 55].

Obesity is associated with atherosclerosis, abnormalities in the coronary microvasculature and as a result increased risk for CAD [56, 57]. Furthermore, excess adipose tissue accumulation leads to major hemodynamic changes, including increased blood volume and blood pressure, cardiac output, as well as myocardial wall stress [58]. Moreover, ectopic pericardial and epicardial fat induces myocardial fat accumulation, resulting in local inflammation, macrophage infiltration, cytokine gene expression, thus leading to subsequent myocardial fibrosis, and cardiomyocytes hypertrophy. Of note, concentric LV remodeling and LVH, right ventricular dilatation and right ventricular dysfunction have been reported among patients with obesity [54]. Considering that patients with obesity present impaired systolic and diastolic cardiac function, they are more likely to develop HF [59]. Interestingly, obese patients have a 56% higher risk of developing HFpEF [60].

3. The effect of exercise training on left ventricular remodelling among patients with cardiometabolic risk factors

3.1. In patients with hypertension

According to current literature, exercise training leads to substantial reduction in resting systolic and diastolic blood pressure, as well as in LVH among hypertensive patients [61, 62], as presented in *Table 1*. Additionally, recent studies indicate that moderate and regular physical activity reduces significantly total peripheral resistance [63, 64]. Exercise-mediated hemodynamic changes include also increased cardiac output along with redistribution of blood flow to muscular territories [65]. So far, there is evidence that exercise training may reduce LV hypertrophy in parallel with systolic and diastolic blood pressure improvement [66].

Turner et al. were from the first to report that that exercise training may induce regression of LVH and LV concentric remodeling among patients with mild or moderate hypertension [67]. In more details, exercise training improved aerobic efficacy by 16% and decreased substantially systolic and diastolic blood pressure, LV wall thickness, as well as LV mass index. Of note, LVH regression was mainly attributed to the reduction of the systolic blood pressure [67]. Indeed, the evidence that exercise training improves significantly systolic and diastolic blood pressure among patients with mild or moderate hypertension is well documented so far [68, 69].

Furthermore, low-fit individuals with hypertension seem to have higher LV mass index when compared to the moderate and high-fit individuals [62]. In this randomized controlled trial, 16 weeks of aerobic exercise led to a substantial regression of LV mass and thickness of the interventricular septum, which were mainly attributed to linear reduction in systolic and diastolic blood pressure [62]. Similarly, regular exercise training results in lowering blood pressure, LV mass index, as well as exercise capacity among patients with borderline or mild hypertension [66]. Exercise-mediated decreased posterior wall and intraventricular septal thickness are also found in hypertensive patients [70]. Moreover, there is also evidence that 1-MET increase in workload offers a 42% reduction in the risk of LVH [71]. Of note, regular physical activity seems to prevent the development of LVH among hypertensive patients at stage 1 [72]. More specifically, patients in physically active group were less likely to develop LVH when compared to those following a sedentary lifestyle, after a median follow-up of 8.3 years.

3.2. In patients with type 2 diabetes

So far, there is evidence that exercise training may improve both LV systolic and diastolic function in patients with diabetes, resulting in favorable changes in stroke volume, LVEF, end-systolic volumes, as well as LV filling [73]. Both endurance and combined endurance and resistance exercise training beneficially affect cardiovascular parameters among patients with T2D [74]. According to a randomized clinical trial, high intensity intermittent training (HIIT) seems to improve substantially cardiac function and structure among patients with T2D, resulting finally in a positive cardiac remodeling [75]. In more details, this type of 12-month exercise interventional program ameliorated both LV mass and systolic function when compared to standard care. Of note, these changes were accompanied by modest improvements in glycemic control.

Furthermore, Otten et al. reported that supervised exercise training (3weeks/hour) along with paleolithic diet (based on vegetables, fruits, berries, nuts, seafood, eggs, fish and lean meat with a high restriction of dairy products, cereals, legumes, refined fats, added sugar and salt) resulted in favorable metabolic and cardiac changes with a decrease in triglycerides levels and LV mass to end-diastolic volume ratio and an increase in LVEDV and stroke volume, among overweight and obese patients with T2D [76]. Similarly, exercise training seems also to improve diastolic function among patients with T2D. In a randomized clinical trial, a 12-week supervised aerobic exercise training program improved diastolic function in the absence of any major effects on LV remodeling, perfusion, or aortic stiffening, among asymptomatic young patients with T2D [77]. Interestingly, exercise-mediated favorable changes in LV remodeling index seems to be the best predictor of improvement in LV diastolic function after the lifestyle intervention program including increased physical activity among patients with T2D and CAD [78].

3.3. In patients with type obesity

Physical activity improves LVH among patients with obesity and hypertension. In more details, higher physical activity was associated with a reduction in LV mass index and an improvement in LVH, as well as cardiac biomarkers such as N-terminal pro-atrial natriuretic peptide (NT-pro BNP) and mid-regional sequence of pro-A-type natriuretic peptide (MR pro-ANP) [79]. Similarly, a decrease in triglycerides levels and LV mass to end-diastolic volume ratio and an increase in LVEDV and stroke volume, are reported among overweight and obese patients with T2D who participated in supervised exercise training programs [76]. Of note, the beneficial effects of exercise training on the reduction on LV mass are apparent regardless of whether the obese patients are normotensive or

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hypertensive. More specifically, Himeno et al. reported that mild exercise along with mild hypocaloric intake resulted in significant weight and LV mass reduction among obese patients, after a 12-week intervention period [80]. Indeed, LV mass was significantly decreased among obese patients regardless the presence of hypertension or not, whereas significant changes were found in the systolic, diastolic, and mean blood pressure. These data provide evidence that exercise-mediated reduction in LV mass is not only attributed to reduction in blood pressure and weight loss, but also to further mechanisms such as improved cardiac autonomous function [81], myocardial metabolism and metabolic flexibility, as well as reduced LV stiffness [82].

Main studies evaluating the effect of exercise training on LV remodeling in patients with cardiometabolic risk factors, such as hypertension, T2D, and obesity are summarized below in *Table 1*.

Table 1. Main studies evaluating the effect of exercise training on LV remodeling in patients with cardiometabolic risk factors, such as hypertension, type 2 diabetes, and obesity.

Author	Type of study	Patient Characteristics	Main findings
Zanettini et al. [61]	Prospective cohort study	•14 sedentary patients with untreated diastolic BP (90-104 mmHg) •12-week supervised exercise program	•Exercise-mediated increase in aerobic fitness significantly reduced resting systolic and diastolic BP, mean systolic and diastolic 24-hour BP, as well as LV mass index.
Kokkinos et al. [62]	Randomized controlled trial	•46 male patients with severe hypertension •35-76 years of age •16 or 32-week exercise program plus antihypertensive medication or antihypertensive medication alone	•Diastolic BP decreased in the patients who exercised, whereas it increased slightly, in those who did not exercise. •Thickness of interventricular septum, LV mass, and mass index decreased significantly only in the patients who exercised.
Turner et al. [67]	Prospective cohort study	•11 patients with mild to moderate hypertension vs 7 sedentary hypertensive patients as controls •65.5± 1.2 vs 68.5±1 years of age •6.8±3.8- month exercise program	•Exercise training decreased systolic and diastolic BP, LV wall thickness and mass, as well as wall thickness-to-radius. •Only the reduction in resting systolic BP was correlated significantly with the regression of concentric remodeling.
Pitsavos et al. [66]	Randomized controlled trial	•40 patients with borderline to mild hypertension •53±7 years of age •16-week exercise aerobic program or standard care	•Systolic and diastolic BP, as well as heart rate were significantly lower in the exercise group compared to the control group. •LV mass index decreased significantly only in the exercise group.
Palatini et al. [72]	Prospective cohort study	•454 patients with stage 1 hypertension •33.1±8.4 years of age •median follow-up of 8.3 years	•Physically active groups were less likely to develop LVH than sedentary group. •BP declined in physically active patients and slightly increased in the sedentary peers.
Cassidy et al. [75]C	Randomized controlled trial	•28 patients with type 2 diabetes •61±9 vs 59±9 years of age •12-week HIIT or standard care	•HIIT improved LV wall mass and stroke volume. •Early diastolic filling rates increased, and peak torsion decreased in the treatment group.
Otten et al. [76]	Randomized controlled trial	•22 overweight and obese subjects with type 2 diabetes •61(58–66) vs 59(52–64) years of age •12-week PD-EX vs PD and standard care	•Significant decreases in LV mass to EDV ratio was observed in the PD-EX group. •LVEDV and stroke volume increased significantly only in the PD-EX group.
Gulsin et al. [77]	Randomized controlled trial	•87 patients with type 2 diabetes and 36 matched controls •50.5±6.5 vs 48.6±6.2 years of age •12-week supervised aerobic exercise training vs low-energy MRP diet vs routine care	•Supervised aerobic exercise training program improved diastolic function in the absence of any major effects on LV remodeling, perfusion, or aortic stiffening. •MRP resulted in weight loss, and improved blood pressure, glycemia, LV mass/volume, and aortic stiffness but not diastolic function.
Kamimura et al. [79]	Retrospective cohort study	•1,300 African Americans with preserved LVEF (>50%) •63 (57, 69) years of age •physical activity was calculated as 3*heavy activity hours + 2*moderate activity hours + slight activity hours/day	•Higher physical activity index was independently associated with lower LV mass. •Higher physical activity index was associated with lower LV mass index more in obese or hypertensive participants compared with non-obese or non-hypertensive participants.

Himeno et al. [80]	Prospective cohort study	•11 obese and hypertensive patients and 11 obese and normotensive patients •37±11 vs 35±7 years of age •12-week weight-reduction program consisted of mild exercise and mild hypocaloric intake	•Systolic, diastolic, and mean BP were significantly reduced only in the hypertensive group. •LV mas was significantly reduced both among hypertensive and normotensive obese patients.

3.4. In patients with coronary artery disease

LV remodeling following acute myocardial infraction (AMI) is a complex process characterized by fibroblast proliferation, collagen deposition, scar formation, as well as ventricular expansion, resulting in LV dysfunction and HF, thus negatively affecting long-term prognosis in these patients [83, 84]. The beneficial effect of exercise training on cardiovascular mortality and morbidity, functional capacity and quality of life in patients with AMI is quite well documented so far [85]. Plenty studies demonstrate that exercise training affects favorably LVH and LV remodeling. Interestingly, exercise training might reverse LVH to normal status or at least undergoing concentric remodeling [86]. Moreover, there is evidence that training, especially aerobic, improves LVEF, decreases end-diastolic volume (EDV) and end-systolic volume (ESV) [87, 88]. According to a large meta-analysis, exercise training leads to an increase in LVEF, as well as reduction in ESV and EDV in clinically stable post-MI patients [89]. Of note, the greatest benefits in LVEF, ESV and EDV are occurring when exercise training starts earlier following MI and lasts longer than 3 months, with each week of training delay to require one additional month of training to achieve the same level of improvement in LV remodeling and the comparable reduction in volumes. Moreover, a decrease in plasma NT-pro-BNP and increase in peak early mitral flow velocity have been also observed post-training [87, 88, 90]. Moreover, there is evidence that systematic exercise and participation in cardiac rehabilitation programs may significantly improve the cardiorespiratory function, exercise ability, and quality of life in patients with ischemic and nonobstructive coronary arteries (INOCA) [91]. Nevertheless, prolong endurance exercise training seems to have detrimental effect on LV systolic and diastolic function.

The beneficial effect of exercise on LV remodeling and cardiopulmonary rehabilitation in LV dysfunction among post-MI patients is also verified by Zhang et al. In this large meta-analysis, it was reported that the greatest benefit of exercise on LV remodeling and cardiopulmonary capacity rehabilitation, as assessed by peak oxygen uptake (VO2), was observed, when exercise was initiated in the acute phase after MI, without an increase in the incidence of MACEs [92]. Indeed, during the healing phase after acute MI, the beneficial effects of exercise training on LVEF, LVESD and peak VO2 weakened compared to the acute phase. Even HIIT seems to improve exercise capacity and quality of life without any detrimental effects on LV remodeling [89, 93]. These data imply that secondary prevention along with cardiac rehabilitation programs should be early initiated to achieve the maximal anti-remodeling benefit.

3.5. In patients with heart failure

Obesity and physical inactivity are considered major lifestyle risk factors for the development and progression of HFpEF [94]. Indeed, low fitness has been associated with a great risk of HFpEF than HFrEF [95], whereas patients with HFpEF demonstrate impaired peak VO2 and cardiorespiratory fitness (CRF), which encompass exercise intolerance, when compared to healthy individuals, deteriorating substantially their prognosis [96].

Physical activity and fitness diminish substantially the risk of developing HF, and improve cardiovascular prognosis among patients with established HF [97, 98]. Interestingly, for every 1-MET improvement in functional capacity, the risk of HF is reduced by 17% [99]. Participation in exercise-based cardiac rehabilitation programs seems to increase exercise capacity up to 25%, improves New Yor Heart Association (NYHA) functional status, as well as LV remodeling and hypertrophy [100]. Of note, there is evidence that the beneficial effect of training programs on symptoms, CRF, left ventricular diastolic and systolic function, as well as quality of life and HF-related hospitalizations are also apparent among patients with HFpEF and HFrEF [101–105]. Moreover, it is also reported that even endurance training reverses adverse cardiac remodeling, and reduces ESV and EDV, thus improving both systolic and diastolic dysfunction in patients with HFrEF [106]. Similarly, high-intensity training affects beneficially exercise capacity and quality of life, with no detrimental changes in LV remodeling among patients with HFrEF [107]. As a result, patients with higher levels of physical activity experience less adverse cardiac events [108].

According to current literature, exercise training has been associated with a substantial improvement in LV diastolic function, [95, 98]. Moreover, it has been reported that exercise reduces LV volumes, which are surrogate markers of LV concentric remodeling or LVH, in patients with HFpEF, whereas exercise training is also correlated with improved measures of CRF. These data demonstrate the pathophysiologic role of LV concentric remodeling contributing to impaired CRF and exercise intolerance in patients with HFpEF and imply that the exercise-meditated improvement in LV remodeling may improve CRF in patients with HFpEF, thus providing novel therapeutical implications [109].

4. Pathophysiological mechanisms of exercise-mediated favorable cardiovascular outcomes

One possible explanation for the favorable effect of exercise training on LV remodeling is the reduction in blood pressure [110]. Afterload reduction to LV mediated by lowering blood pressure has been proposed as a possible mechanism leading to regression of LVH and concentric remodeling [67, 111]. Additionally, favorable effects of exercise training on cardiovascular system are mainly attributed to changes in vascular function, cardiac energy metabolism, autonomic balance, including improvement in endothelial dysfunction, arterial and LV stiffness, myocyte calcium handling, mitochondrial function, systolic and diastolic wall stress, cardiac output, and oxygen extraction in the active skeletal muscles. Moreover, increased vasculogenesis though activation of endothelial progenitor cells, ameliorates ischemia and reperfusion injury [64, 65, 112–116]. Exercise modifies shear stress conditions and modulates further the bioavailability of endothelial nitric oxide (NO), which limits oxidative burden, thus promoting vasodilation and improving vascular endothelial function [64]. Specifically, improvement of endothelium-dependent relaxation is mainly regulated by decreased NO scavenging by reactive oxygen species (ROS) and increased vascular NO production and release.

Furthermore, exercise is related to decreased chronic, low-grade inflammation, increasing the release of anti-inflammatory peptides and reducing the production of pro-inflammatory cytokines [117]. Moreover, exercise-mediated reduction of myocardial collage has been also described [118]. So, another possible mechanism of exercise-mediated improvement in LV dysfunction is the upregulation of miRNA-29, which has been associated with a drop in collagen gene expression [119]. Moreover, exercise training reduces total peripheral resistance [63], increases parasympathetic activity and restores arterial baroreflex sensitivity (BRS) [120], thus ameliorating LVEF and heart rate variability [121]. Nevertheless, plenty pathophysiological mechanism responsible for exercise-mediated regression of LVH remain still unclear.

5. Recommendations and new perspectives

According to 2019 American College of Cardiology (ACC) in collaboration with (AHA) Guideline on the Primary Prevention of CVD, in general, healthy individuals should undergo at least 150 minutes/week of accumulated moderate-intensity physical activity. Otherwise, 75 minutes/week of vigorous-intensity physical activity to reduce the risk of atherosclerotic CVD [122]. In total agreement to previous recommendations, European Society of Cardiology (ESC) highlights that additional benefit is achieved by doubling the previous exercise duration, with multiple sessions of exercise carried out throughout the week [123, 124]. More specifically, hypertensive patients should be advised to participate in at least 30 min of moderate- intensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5–7 days per week [125]. Performance of resistance (and especially isometric) exercise on 2-3 days per week can also be advised. However, patients, who are unable to perform the recommended and desirable regular physical activity, should be encouraged to participate in training programs even below the target goal, considering that the exercise-mediated benefit for the cardiovascular system still remains. Therefore, healthcare professionals should offer patient-focused counseling, encourage their patients to participate in well-organized supervised training programs and help them to optimize their physical activity status, considering the favorable effect of exercise on cardiometabolic risk factors and LVH regression [122].

The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool is an interactive, digital training and support system, which aims to help sports medicine specialists, family physicians, cardiologists, and other medical specialties, to prescribe clinically effective and medically safe exercise training programs among patients with established CVD or cardiometabolic risk factors [126]. In further detail, this website application will analyze patient characteristics, the presence of CVD or cardiometabolic risk factors, contaminant medication or other clinically relevant medical information, so as to generate the most suitable exercise training program for each patient, discouraging certain types of exercise and providing personalized safety advice. Of note, individualized recommendations regarding exercise training intensity, frequency, duration, type, session, as well as additional exercise training modalities will be offered to the patient [126].

6. Conclusion

Improving exercise capacity and optimizing safety of cardiorespiratory programs play a pivotal role in promoting cardiovascular health. Exercise training enhances functional capacity, muscle strength and endurance, cardiac function and cardiac-related biomarkers, as well as quality of life, thus improving substantially cardiovascular prognosis. Exercise training exerts beneficial changes to LV remodeling, thus improving cardiac function and structure among patients with cardiometabolic risk factors. These favorable effects are mainly attributed to positive hemodynamic changes in vascular function, cardiac energy metabolism, and autonomic balance. Therefore, a comprehensive and more personalized approach should be taking into account based on the individual behavioral habits and wishes, cardiovascular profile and needs. It is of major importance that guided, detailed and personalized exercise prescription should be offered by all physicians so as to achieve better treatment, as well as health outcomes.

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