Mechanisms behind exercise intolerance in Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is becoming one of the most prevalent cardiovascular disorders in elderly and growing out of proportion in comparison to heart failure with reduced ejection fraction (HFrEF). The pathophysiological mechanism behind HFpEF is still largely unclear and due to this lack of knowledge there has yet to be found an optimal treatment. The predominant feature of HFpEF is exercise intolerance and with this a reduction in quality of life. Previously, research has focused on a central cardiac mechanism and the development of exercise intolerance. The decrease in exercise tolerance was primarily due to a poor cardiac output. However, research has recently shown that exercise intolerance is not primarily due to a central cardiac mechanism but due to a peripheral mechanism. This peripheral mechanism primarily focuses on the muscle adaptations in HFpEF, which largely accounts for the decrease in peak VO2 and thus exercise intolerance. Moreover, exercise training seems an effective treatment for improvements in exercise tolerance in HFpEF patients even in the absence of changes in the central cardiac mechanism. Pharmaceutical research also established findings that suggest improvement in exercise tolerance due to alterations in the peripheral mechanism. This introduces a paradigm shift to focus more on the peripheral mechanism associated with exercise intolerance in HFpEF and new possibilities for effective treatments.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is characterized by an increase in cardiac left ventricular stiffness which causes diastolic dysfunction and a decrease in left ventricular relaxation (1). HFpEF results in a major impact on the daily lives of patients, resulting in a decreased exercise tolerance, decreased quality of life and high hospitalization rates (2). In short, HFpEF is a major disease burden. HFpEF has a high morbidity and mortality rate and is prevalent in 50% of the heart failure cases (3). The incidence and prevalence of HFpEF is rising due to many factors, but predominantly due to better diagnostics of HFpEF, aging population and the
epidemic of cardiac and non-cardiac comorbidities (3, 4). In the Framingham heart study it is estimated that approximately 23 million people suffer from heart failure and thus approximately 14 million people suffer from HfPEF (5). It should be noted that accurate estimation of HfPEF prevalence cannot be made due to lack of standardization in diagnostic criteria and due to the heterogenic characteristics of HfPEF. There are significant differences in outcomes in relative prevalence due to different study designs (3, 4). HfPEF is predominantly a disease of the elderly, more a female than a male disease in a 2:1 ratio (6) and with a high prevalence of comorbidities like obesity, hypertension, chronic obstructive pulmonary disease and chronic kidney disease (7). The true cause of HfPEF is still unclear and it has been hypothesized and partly proven that HfPEF has multifactorial causes with a heterogenic profile (8).

Due to the complexity in the origin of HfPEF it has also been challenging to find effective treatments. Many treatments focused on the hypothesized pathophysiological mechanism for HfPEF, with most outcomes considered as disappointing. Kraaij et al. concluded that quality of life in heart failure patients is generally more important than longevity and quantity of life in HfPEF patients (9). One of the major limiting factors in the perception of quality of life is being autonomous and the execution of tasks in daily living (10). One of the conditions to perform tasks of daily living and being autonomous is that people can perform physical activity including exercise. However, one of the major symptoms of HfPEF is exercise intolerance, which greatly decreases quality of life (11). As stated before, research primarily focuses on the pathophysiological processes in long prospective and randomized controlled trials, but HfPEF patients need improvement of their symptoms as soon as possible. Currently, there is a knowledge gap in the field of cardiac research on "How pharmaceutical interventions and non-pharmaceutical interventions can improve exercise capacity in HfPEF patients?" The improvement of exercise capacity is relevant because it limits the decrease in quality of life and even improves the pathophysiological status, since exercise decreases the impact of comorbidities on the heart (12). This review will provide an overview on the hypothesized pathophysiological processes implicated in HfPEF, the relationship between HfPEF and exercise intolerance, pharmaceutical interventions with respect to exercise in HfPEF and the non-pharmaceutical interventions for exercise in HfPEF.

2.1 Systemic inflammation in HfPEF

The state of systemic inflammation can lead to myocardial stiffness by endothelial dysfunction of the heart. The endothelial dysfunction of the heart is caused by an increase in expression of adhesion molecules like vascular cell adhesion molecules (VCAM) and E-selectin, which leads to activation and migration of circulating leukocytes into the heart by crossing the endothelium (13). Because of this leukocyte migration, the coronary microvascular endothelial cells produce reactive oxygen species (ROS) through initiation of nicotinamide adenine dinucleotide phosphate oxidases (14). The reactive oxygen species inhibit the nitric oxide (NO) bioavailability for the adjacent cardiomyocytes (14).

2.2 The effects of low nitric oxide in HfPEF

Low NO bioavailability leads to reduced cyclic guanosine monophosphate production (cGMP) by soluble guanylate cyclase which will lead to low protein kinase G (PKG) activity (15). In turn, low PKG levels will lead to hypertrophy of the myocardial wall by cardiomyocyte hypertrophy. Moreover, hypertrophy of the left ventricle establishes a reduction in myocardial relaxation (15). Furthermore, a low NO bioavailability leads to the diversion of NO to peroxynitrite by superoxide anion (16). Peroxynitrite is known for its effects on cardiomyocyte contraction. Peroxynitrite decreases cardiomyocyte contraction by increasing protein phosphatase 2a activity, which in turn reduces phospholamban phosphorylation. This leads to a reduction of calcium uptake by the sarcoplasmic reticulum and increases diastolic cytosolic calcium (16). Since the diffusion of calcium from the cardiomyocytes to the sarcoplasmic reticulum is necessary for relaxation, relaxation cannot be achieved and leads to high resting tension at high pacing frequencies (17).

2.3 Cardiomyocyte stiffening and fibrotic remodelling in HfPEF

Titin is a protein that acts like a spring and is responsible for early diastolic recoil and late diastolic distensibility of the cardiomyocytes (18). This spring-like...
characteristic of titin is modified by PKG. Low PKG activity causes hypophosphorylation of the N2B segment of titin; this enhances the diastolic recoil and distensibility during diastole and leads to a high resting tension and a reduction in cardiac output (CO) (18). Finally, myocardial stiffness in HFpEF is also caused by collagen deposition due to differentiation of fibroblasts into collagen-producing myofibroblasts. The differentiation is caused due by release of TGF-beta from monocytes upon their migration into the microvascular endothelium. This process is called fibrotic remodelling (15).

3. HFpEF and exercise intolerance

The primary chronic symptom of both HFrEF and HFpEF is exercise intolerance. Exercise intolerance is the condition wherein people have a diminished ability to perform physical exercise at what is contemplated to be in normal duration or intensity or both (19). Exercise intolerance can be measured objectively as a decreased peak oxygen uptake during exercise. Exercise intolerance is strongly related to the prognosis of HFpEF and the reduction in quality of life. Furthermore, the exercise capacity is related to exercise intolerance and the exercise capacity is the maximum amount of physical exertion that a person can sustain (20). Two theories about mechanisms associated with exercise intolerance in HFpEF will be explored in the next part of this review.

4. Central mechanism behind exercise intolerance

One of the main problems of HFpEF is the decrease in cardiac output (CO) due to limited ventricular filling as a result from diastolic dysfunction. Exercise intolerance is a major symptom for the diagnosis of HFpEF and treatment is focused on the improvement of exercise tolerance to increase quality of life and possibly prevent further deterioration of HFpEF (21). The heterogenetic character of HFpEF poses a big problem in the identification of all the pathophysiological steps in HFpEF, but improving the exercise tolerance and the general physical fitness can inhibit further deterioration.

4.1 Peak VO2 consumption and cardiac output in relation to exercise intolerance

Exercise capacity can be quantified by several tests which measure the cardiopulmonary capacity during exercise. The main focus during these tests is the gas analysis to determine the peak exercise oxygen consumption (VO2max), which is the main measurement to determine the cardiopulmonary fitness during respiratory exercise testing (22). Many studies (23-26) use the Fick equation to determine the VO2max, which is determined by 3 factors that all take part in determining the cardiorespiratory fitness. The 3 factors are: heart rate (HR), stroke volume (SV) and arteriovenous oxygen difference (A-VO2) which add up to the following; VO2max = CO x (A-VO2 ) = (HR x SV) x (A-VO2) (27). However, there is still no conclusion on which factor in the Fick equation causes the decrease in VO2max.

Several studies have concluded that the reduction in VO2max is probably caused by a decreased cardiac output (24-26). The reduction in cardiac output is due to stiffening of the left ventricle. This leads to a decrease in left ventricular end-diastolic volume and thus less filling of the left ventricle, which results in a smaller volume of blood pumped into the systemic circulation.

However, exercising muscles have increased metabolic needs and thus need an increase in blood volume with soluble nutrients and oxygen, to supply the working muscles with enough substrates and eliminate metabolic waste products. When the blood and metabolite supply is insufficient, muscles tend to fatigue faster and this leads to exercise intolerance (28). Furthermore, the Frank-Starling mechanism is also limited. The Frank-Starling mechanism states that when the blood volume that enters the ventricle increases, this will lead to an increased stretch of the cardiac walls and thus creates an increased expansion during the diastolic filling, which ends in an increased contraction force and thus a higher stroke volume during the systole (29). This does not happen in patients suffering from HFpEF, due to the diastolic stiffness which hampers the increase in left ventricular end-diastolic volume that normally increases during exercise, despite greater filling pressures (24, 25). In the end, during exercise, stroke volume ceases to increase while the diastolic pressure increases and this will lead to fatigue and exercise intolerance.

4.2 PCWP and lung edema in relation to exercise intolerance
Finally, the lungs also play an important role in the onset and complications following HFpEF. In patients with HFpEF, an increase in the pulmonary capillary wedge pressure (PCWP) causes lung edema, this in turn limits O2 diffusion (30). Pulmonary capillary wedge pressure is measured using a catheter to determine the left arterial pressure (30, 31). When the left atrial pressure is increased in HFpEF, there is an increased likelihood that blood flows back into the pulmonary capillaries and thus causes lung edema. In turn, lung edema causes a decrease in oxygen diffusion and thus a lower blood oxygen content going to the heart and eventually into the systemic circulation (31).

4.3 Downward spiral theory

There is a potential risk to end up in a downward spiral when becoming exercise intolerant due to HFpEF. For example, obesity exacerbates exercise tolerance and exercise capacity in HFpEF. This in turn leads to an increase in sedentary behaviour and a sedentary lifestyle is associated with worsening of obesity. This vicious circle needs to be interrupted to prevent further deterioration of the HFpEF condition.

In short, there has yet to be found a single cause for the exercise intolerance in patients with HFpEF, but just as the biological mechanism underlying the inflammation reaction of the cardiomyocytes, the mechanism behind exercise intolerance is multifactorial and heterogenic. The reduced cardiac output partly causes exercise intolerance, however the complete reduction in exercise tolerance cannot solely be attributable to a reduction in cardiac output.

![Figure 1: Central mechanism behind exercise intolerance in HFpEF.](image)

**Obesity and other consequences of the metabolic syndrome lead to a proinflammatory state. This state causes ventricular stiffness in the heart. The left ventricular stiffness increases the diastolic filling pressure and consequently also the pulmonary capillary wedge pressure. The increase in these two aspects leads to lung edema, which is a limiting factor for oxygen diffusion. Consequently, the blood contains less oxygen and the reduced cardiac output further decreases oxygen delivery to the active muscle tissue. This leads to a decrease in exercise capacity which in turn can cause deterioration of obesity or other consequences of the metabolic syndrome like hypertension, which completes the downward spiral in HFpEF. All these factors contribute to the central mechanism behind exercise intolerance in HFpEF.**

5. Peripheral mechanism behind exercise intolerance

Recently, a new theory has emerged about the causes of exercise intolerance in HFpEF patients. This new theory focuses on the adaptations associated with HFpEF on muscle level. This new paradigm shifts the attention from a central mechanism to a peripheral mechanism, with regard to exercise intolerance in HFpEF. This also provides new ways to develop possible treatments for improving exercise tolerance.

5.1 Arterial-venous oxygen difference in exercise intolerance
A meta-analysis of Pandey et al. concluded that exercise training in patients with HFpEF improves cardiorespiratory fitness and quality of life, following a fitness test and the Minnesota living with heart failure questionnaire (12). Interestingly, these improvements were established without significant changes in left ventricular systolic or diastolic function. The cardiorespiratory fitness is the ability of the heart to pump blood to the working tissues to meet their increased oxygen needs, during exercise (32). Exercise training increased peak oxygen uptake and prevented dyspnoea, and thus increased exercise tolerance in patients with HFpEF (12). Since the improvements are without change in resting diastolic or systolic function, exercise training may improve cardiorespiratory fitness through mechanisms independent of left ventricular function.

These findings suggest that exercise training may improve exercise tolerance by a peripheral mechanism. This might be due to an increase in peripheral oxygen extraction in HFpEF. Active muscles cause an increase in arterial-venous oxygen difference (A-VO2), which shows that the muscles more effectively take up and use oxygen from the blood to improve their oxidative capacity (33). Another large randomized control trial showed, in a study population (N=104) with different HFrEF (N= 48) and HFpEF (N=56) patients, that impaired peripheral oxygen extraction was the predominant limiting factor in exercise capacity in 40% of the HFpEF cases (34). On the contrary, in HFrEF, only 2% of the patients were limited in exercise capacity due to limited peripheral oxygen extraction.

Haykowsky, et al. established similar findings in their study. Haykowsky, et al. (23) concluded in a randomized control trial of 4 months, with an exercise group and a control group (ET N=22 and control N=18), that peak A-VO2 was higher in the intervention group and accounted for almost all the improvements in peak VO2. These authors showed that the improvement following 4 months of moderate-to vigorous exercise was not significantly due to an increase in CO.

5.2 Arterial stiffening further deteriorates exercise intolerance

Changes in arterial function are established in HFpEF patients. There is impairment in peripheral arterial endothelial function in patients with HFpEF. The stiffening of arteries is an effect of normal aging, but can be exacerbated by HFpEF (35). In HFpEF there is a reduction in aortic distensibility and carotid artery distensibility (35). The stiffening may be due to the activation of renin-angiotensin system and the adrenergic system, which can lead to hypertrophy of the vascular wall structure. Furthermore, endothelial dysfunction also diminishes the vasodilation capacity of the arteries. Finally, atherosclerosis may also lead to a decreased distensibility of the arteries (35). Moreover, this stiffening impairs blood flow to active muscles during exercise, which goes beyond that of normal aging (36). So, changes in peripheral arterial function may result in an ineffective redistribution of the CO to the active muscles, which lead to exercise intolerance.

However, many studies did not conclude the above. For example, Haykowski, et al. concluded that blood flow to the legs in HFpEF patients was not significantly impaired compared to healthy elderly (37). Kitzman, et al. conducted a randomized controlled trial for 16 weeks, investigating 63 HFpEF patients in their peak VO2 response to exercise training. The outcomes of this study showed that exercise training improved peak VO2 response, but this improvement was achieved without altering endothelial function or arterial stiffness (38). These findings suggest that improvement in peak VO2 is probably due to increase in skeletal muscle perfusion or oxygen utilization by the muscle rather than improvements in cardiac output.

Yet, most of these studies are done by determining the flow-mediated dilation in large conduit arteries and not in the microvasculature to determine the extent of microvascular endothelial dysfunction. A study conducted by Borlaug, et al. introduced that microvascular endothelial dysfunction was correlated with a reduced exercise capacity (39). A decreased microvascular reserve is related to decreased A-VO2 to active muscle. This decreased exchange of oxygen leads to exercise intolerance. Many comorbidities like obesity, hypertension and diabetes are associated with muscle microvascular dysfunction.

5.3 Difference in muscle composition in HFpEF

HFpEF is associated with a change in muscle composition in terms of muscle fiber ratio’s and oxidative capacity of the muscle. These changes
contribute to the reduction in exercise intolerance in HFrEF patients (40, 41).

Esposito, et al. established in HFrEF patients a reduction in oxygen diffusion to the muscles, which, similar to HFrEF, leads to a reduced muscle function and exercise intolerance (42). Moreover, in HFrEF all oxidative pathways in skeletal muscle are compromised. There is a decrease in type 1 (oxidative) muscle fibers and the associated oxidative enzymes, which leads to a decrease in oxidative capacity (42). Furthermore, there is also a decrease in mitochondrial content in the muscle fibers and thus in mitochondrial mass and function (43). In HFrEF, similar obstructions are found, including a reduction of type 1 oxidative muscle fibers and a reduced capillary-to-fiber ratio (44).

Additionally, a study conducted by Seiler, et al. tried to establish the differences in muscle alterations in HFrEF and HFrEF patients. They conducted an animal study with rats, wherein HFrEF was caused by ligation of the left anterior descending coronary artery to induce a myocardial infarction and HFrEF rats were fed a high salt diet for over 28 weeks to induce diastolic dysfunction and the pathophysiology of HFrEF. The muscle alterations in HFrEF rats were associated with an increase in atrophy, elevated oxidative stress and decreased mitochondrial respiration. However, these changes were not established in skeletal muscles of HFrEF rats. This leads to the assumption that muscle wasting plays a greater part in HFrEF than HFrEF. This study also concluded that the A-VO2 is an independent predictor of exercise capacity in HFrEF and microvascular dysfunction in the form of; increased intermuscular fat disposition, fiber type shift and reduced capillary-to-fiber ratio play a major role in exercise intolerance (45).

5.4 Fat infiltration and lean body mass in exercise intolerance in HFrEF

Since fat infiltration in muscle is a main symptom of diabetes and obesity and causes reduced exercise capacity in these people, it is possible that fat infiltration also contributes to exercise intolerance in HFrEF patients (40).

Haykowsky, et al. concluded a decrease in body lean and leg lean mass in HFrEF patients, compared to healthy age-matched subjects. Moreover, there was a reduction in peak VO2 levels and this was associated with a reduced lean leg mass (46). Therefore, it is plausible that a reduced lean body mass in HFrEF patients further improves exercise tolerance compared to a normal reduction in peak VO2 associated with normal aging (41).
muscle fatigue (50). This in turn leads to a reduced exercise capacity. This study is performed with a small population and therefore future studies need to elaborate on this topic, with a bigger study population. However, this conclusion is supported by other randomized controlled trials, but again based on a small research population (47).

5.5 Haemoglobin in the blood and oxygen extraction in relation to exercise intolerance

In a group of 111 heart failure patients, the main limitation for exercise capacity in those with HFrEF (N=56) was left atrial enlargement, whilst for HFpEF (N=55) patients the main limitation was systolic shortening and low haemoglobin content (11). Unfortunately, this study only addressed the response of echocardiographic measurements to exercise and did not include peripheral measurements of oxygen extraction at muscle level.

Interestingly, Cohen et al. found that treatment with erythropoietin increased haemoglobin content and consequently improved exercise capacity and quality of life in HFpEF patients with anaemia. This was thought to be due to a better control of anaemia, but the treatment with erythropoietin could also independently lead to an increase in exercise capacity in HFpEF patients without anaemia. However, the safety and tolerability of the use of erythropoietin therapy still needs further exploration, and currently the FDA (Food and Drug Administration) states that it can only be used while under extensive monitoring (51).

5.6 Downward spiral theory

Based on the above mentioned findings, a similar downward spiral model can be made for the peripheral mechanism associated with exercise intolerance in HFpEF. In short, HFpEF related muscle adaptations lead to a decreased exercise tolerance, which in turn leads to a decrease in physical activity. A decrease in physical activity is associated with an increase of sedentary behaviour, which is associated with an increased incidence of obesity. This downward spiral further deteriorates exercise tolerance and can lead to a pro-inflammatory state which is associated with HFpEF.

Figure 3: Peripheral mechanism behind exercise intolerance in HFpEF

Exercise intolerance is mainly caused by a reduction in A-VO2 difference, which resembles a reduction in oxygen diffusion. This reduction in in A-VO2 difference is again caused by muscle alterations, which are caused by HFpEF. Moreover, HFpEF is the result of a systemic inflammatory state of the body, which is caused by multiple comorbidities like obesity.

6. Pharmaceutical interventions to increase exercise capacity in HFpEF

Many studies devoted time, effort and money on finding a treatment on the biochemical mechanisms, that malfunction during HFpEF, for the improvement of exercise tolerance. Unfortunately, few pharmacological studies established beneficial effects on the improvement of exercise tolerance.

6.1 Organic nitrate and exercise intolerance

A lot of research has been done with nitrates since nitrate is part of nitric oxide (NO), because nitrate can be reduced to NO (52). One example is a large study of 110 HFpEF patients by Redfield et al., (53) who investigated the effects of nitrate on activity tolerance in HFpEF. The research was a double-blind randomized
trial with placebo groups in which the effects of intake of isosorbide mononitrate were investigated on activity tolerance. The baseline measurement of physical activity was performed using an objective accelerometer and each person was his/her own control group. The isosorbide mononitrate was consumed orally in the form of a pill at a dose of 120 mg/day for 2 to 4 weeks and the same accounts for the placebo. The results were disappointing, since there was a decrease in activity tolerance after the intervention. Besides these findings, the side effects like headaches due to nitrate intake were quite substantial and could have caused a bias in the research. Due to the side-effects, 16 participants (15%) quit during the research period and many more were probably discouraged to exercise or be active. Additional to this limitation, the trial duration was short. In the beginning nitrates looked promising, but due to adverse outcomes and the side-effects, it does not seem a feasible intervention to improve exercise tolerance in people with HFpEF.

6.2 PDE5 inhibitors and exercise intolerance

Another promising pharmaceutical intervention were the PDE5 inhibitors. PDE5 inhibitors are known to inhibit the action of the cGMP-specific phosphodiesterase type 5 on the degradation of cGMP in the heart; this will lead to an increase in cGMP levels in HFpEF patients (54). This in turn was hypothesize to cause systemic/pulmonary vasodilatation and enhanced myocardial relaxation. Many studies are conducted on the effect of PDE5 inhibitors on the increase in cGMP levels and consequently improving exercise tolerance, but with contradictory results. Guazzi et al. performed a randomized controlled trial to examine the effects of the PDE5 inhibitor sildenafil on hemodynamics and exercise capacity and concluded that treatment with sildenafil improved exercise capacity (55). However, most studies showed a non-significant improvement in exercise capacity while using PDE5 inhibitors. For example, a study performed by Redfield et al. concluded that exercise capacity was not increased while using PDE5 inhibitors as a treatment (56). The contradictory results may be due to the methodological differences between the studies. Redfield et al. used a bigger research population compared to Guazzi et al. (n = 216 vs. n = 44). Then again the study of Guazzi et al. had a duration that was twice as long compared to Redfield et al. (52 weeks vs. 24 weeks). But the most profound difference between the two studies is the fact that Guazzi et al. performed their study with a subgroup of HFpEF and thus is not generalizable to the whole population who suffers from HFpEF, while Redfield et al. did not perform this kind of selection. Also interesting is the fact that within these studies there is no significant increase in cGMP after treatment with sildenafil, and thus the hypothesis is that reduced cGMP levels are not due to breakdown of cGMP by PDE5. There is likely something wrong with the cGMP production.

6.3 Soluble guanylyl cyclase stimulators and exercise intolerance

Soluble guanylyl cyclase (sGC) stimulators are another way of topping up reduced cGMP levels in HFpEF hearts. SGC stimulators enhance the activity of guanylate cyclase, which is the enzyme that synthesizes cGMP from GTP (57). Recently, a few studies have focused on the enhancement of cGMP by sGC stimulators. The results of these studies show improvement of normal cardiac functioning, increased protection against cardiac dysfunction and prevention of cardiac remodelling by maintaining PKG levels (58, 59). Moreover, sGC stimulators seem to work independently of nitric oxide, this is important since there is a problem with cGMP production in HFpEF (58, 59). Further research is needed to provide conclusive evidence in human, compared to these hypothetical theories based on human and animal studies.

6.4 Inorganic nitrate and exercise intolerance

Recently, targeting the inorganic nitrate-nitrite pathway was identified as a way to replenish NO bioavailability. Inorganic nitrate can be reduced to nitrite by xanthine oxidase and anaerobic bacteria, whereas nitrite can be further reduced to NO, which is catalysed when tissue oxygen availability is low (60).
Figure 4: Nitrate-nitrite-nitric oxide pathway and improvement of exercise tolerance.

Inorganic nitrate and nitrite are relevant nitric oxide reservoirs, in contrast to organic nitrates, which were discussed above. In previous studies, inorganic nitrate and nitrite were beneficial for endurance athletes to improve their endurance and exercise performance (60). Endurance athletes primarily take in inorganic nitrate by eating and drinking beetroot (juices). After ingestion, the nitrate will be converted into nitrite, stored in a nitrite pool and circulates in the blood. When O2 is low then nitrite can be converted into NO, which in athletes reduces the O2 cost of submaximal exercise and improves exercise tolerance (60). The replenishment of NO is also desirable in patients with HFpEF, since it has been hypothesized that reduced NO bioavailability is one of the causes of HFpEF. Eggebeen et al. performed a study with a relatively small research group (N = 20) of elderly with HFpEF and determined the effects of beetroot juice with inorganic nitrate and a placebo without inorganic nitrate over a 7 day time period. The results showed a significant increase in submaximal aerobic exercise capacity and blood pressure (61). The short time period, in which these effects took place, show the possible great effects of beetroot juice on HFpEF conditions and exercise capacity. The same outcomes are found by Zamani et al. and they showed an increase in exercise vasodilatory and cardiac output reserves (62). Besides these findings, inorganic nitrate also reduced arterial wave reflections, which reflect improvements in left ventricular diastolic function and remodelling (62).

In two double-blind, randomized, placebo-controlled, parallel-group trials with HFpEF patients, Borlaug et al. tried to determine if the intake of inorganic nitrate improved hemodynamics in HFpEF (63, 64). Both trials had a relatively small research group (N = 28 and N = 26), but this is due to the intensive and invasive research program the participants needed to follow. In both studies the subjects underwent cardiac catheterization with simultaneous expired gas analysis in resting conditions and during exercise before and 15 minutes after the treatment with either sodium nitrate, which is an inorganic nitrate, or the placebo (63, 64). In this way Borlaug et al. could measure exercise PCWP, arterial pressure and cardiac output, which are all affected in HFpEF and play a part in exercise intolerance as mentioned above. The results of the first study show that sodium nitrite infusion attenuates hemodynamic derangements that develop during exercise in HFpEF, like increased cardiac filling pressures, exercise-induced pulmonary hypertension and inadequate CO reserve (63). The beneficial effects of nitrite are more pronounced during exercise and this is probably due to the reduction of nitrite into nitric oxide under the condition of hypoxia (63). The second study was performed with inhaled sodium nitrate to limit the invasive characteristics of infusion (64). This study showed a reduction in biventricular and left atrial filling pressures during rest and exercise (64). These outcomes show a substantial improvement in symptom reductions, exercise capacity and quality of life. Further research is needed to show the chronic effects of inorganic nitrite treatments, compared to the outcomes of these acute effect studies.

In short, many studies have been performed to determine the effects of pharmaceutical agents on improving exercise capacity in HFpEF and many had disappointing outcomes. However, some of the most promising findings is the usage of inorganic nitrate and nitrite to improve exercise capacity and sGC stimulators to improve exercise tolerance. Further research needs to be conducted in these areas of interest to unravel more potential beneficial pharmaceutical treatments for HFpEF and its complications.

7. Exercise intervention

The most promising way of improving exercise intolerance in HFpEF is by promoting patients to be
more active and perform physical activity. However, due to the multifactorial origin and complexity of exercise intolerance, it is hard to determine one standard exercise regimen that would benefit all HFpEF patients.

7.1 Central and peripheral improvements following exercise training

Kitzman, et al. conducted a randomized controlled trial to determine the effects of aerobic exercise training on the improvement of exercise intolerance and quality of life. During this study of 16 weeks, 53 HFpEF patients conducted an exercise training program for 3 days per week. This intervention led to an increase in peak VO2 power output, exercise duration, 6-minute walk distance and ventilator anaerobic threshold. Kitzman, et al. also established improvements in quality of life, which was determined by the Minnesota living with heart failure questionnaire (65).

Edelmann, et al. concluded that exercise training with resistance training and endurance training will lead to an increase in exercise capacity and quality of life. The exercise capacity was measured by a peak VO2 test and the quality of life by the Minnesota living with heart failure questionnaire. Interestingly, this study concludes that these benefits of exercise training are due to atrial reverse remodelling and improved of the left ventricular diastolic function (66).

On the contrary, a meta-analysis of 6 randomized control trials performed concluded that the improvement in exercise capacity and quality of life was primarily mediated via a peripheral mechanism, like an improvement in skeletal muscle and arterial function (12). And reviewing the peripheral pathophysiology associated with HFpEF, this theory is probably valid.

7.2 Training intensity to improve exercise tolerance in HFpEF

Training programs conducted for HFpEF and HFrEF originally focus on endurance training at a moderate intensity. Recently, a study conducted by Ellingsen, et al. showed that higher intensity exercise regimes do not change left ventricular remodeling or aerobic capacity more than moderate intensity exercise (67). However, a high intensity interval training (HITT) study in HFpEF patients (N=15), compared the effects of HITT versus moderate-intensity aerobic continuous training on peak VO2. Patients trained 3 days per week for 1 month. Although the research population was small, the results showed a significant improvement in peak VO2 in the HITT group and this was thought to be due to improvements in left ventricular diastolic dysfunction (68).

7.3 Safety of exercise training in HFpEF

HFpEF patients are considered to have a higher risk for major cardiovascular complications during exercise training. Therefore, it is highly recommended to first undergo a graded exercise test before undertaking an exercise regime. This test will determine the safety to participate in unmonitored exercise training (69).

A meta-analysis performed by Taylor, et al. confirms the fact that exercise training confers enhancements in exercise tolerance and quality of life in HFpEF patients. Besides these findings, this study also showed that exercise training is safe in HFpEF patients. There were no deaths or severe inimical effects during or following the training. Once again, this analysis also states that the improvements in exercise capacity are most likely due to peripheral changes, instead of central cardiac changes (70). Due to the improvements in exercise tolerance, high safety and limited adverse effects associated with exercise training, the American college of cardiology states that exercise training is an effective therapy for heart failure (71).

7.4 Combination of dietary intervention and exercise training

In general more than 80% of the HFpEF patients are overweight or obese. Since this is a comorbidity on its own and a risk factor for many other comorbidities associated with the metabolic syndrome, it can be
fruitful to reduce weight as well and by that improving the exercise tolerance (72). A study conducted by Kitzman, et al., intended to determine whether caloric restriction or aerobic exercise capacity improves exercise capacity in HFpEF. The study was performed with 100 obese HFpEF patients. The intervention consisted of 20 weeks of diet or exercise or both with the main outcome improvement in peak VO2. The results showed that the change in peak VO2 was primarily related to an increase in lean body mass and an increase in muscle:intermuscular fat ratio. In the end, body weight decreased by 7% in the caloric restriction group, decreased 3% in the exercise group and 10% in the combination group. So the effects may be additive. Noteworthy, none of the interventions had significantly improved quality of life measured by the Minnesota living with heart failure questionnaire (73).

7.5 Future research

There are 2 large prospective randomized multi-center studies ongoing at the moment. The first one is the OptimEx-CLIN study wherein the objective is to determine the optimal dose of exercise training in HFpEF patients. This study will randomize 180 patients in different exercise intensity regimes for 3 months and 9 months follow-up of telemedically monitored home-based training. The first results are expected in 2017 (74).

The second study is the Exercise training in Diastolic Heart Failure (Ex-DHF) trial, which investigates the effects of 12 months of supervised exercise training on the improvement of clinically important factors in HFpEF like exercise capacity and diastolic function. The exercise training (endurance/resistance training) will be performed under supervision for 3 times a week. This trial is the first to assess the long-term effect of exercise training on different parameters in HFpEF patients (75).

In short, there is no expert consensus on the mode of exercise, but the combination of resistance training and aerobic training seems to be the most beneficial for improving both central and peripheral systems in HFpEF (76). The design of exercise training should still be based on individual’s response to training and measurements obtained during graded exercise testing prior to training. To make training more enjoyable and to improve the adherence to training, the patient’s individual status and preferences should be involved in the construction of a training program (77). These factors lead to a tailored exercise regime which will stimulate the efficiency and safety of the program. In the end, there is evidence that it would be beneficial to combine exercise with a dietary intervention like caloric restriction, to further enhance the improvements of HFpEF (73).

8. Conclusion

In summary, HFpEF is a growing problem in the field of cardiology and public health. The pathophysiological mechanism is still largely unclear, but one of the main symptoms is exercise intolerance which reduces functional capacity and quality of life. Currently, there is a paradigm shift in the understanding of the mechanisms that cause exercise intolerance. First, the main focus was on a central cardiac mechanism which was held responsible for the decrease in exercise tolerance. However, new research has shown that a peripheral muscular mechanism plays a bigger part in exercise intolerance, due to a decreased A-VO2 difference. The multi-factorial complex milieu of HFpEF explains why most pharmaceutical interventions have failed to greatly improve exercise tolerance in HFpEF. Recently, the focus shifts to the effects of exercise training on HFpEF and exercise intolerance. Previous findings in animal studies and HFrEF studies indicated that exercise training might be beneficial for HFpEF as well. These hypotheses are confirmed in HFpEF; exercise training does improve exercise tolerance. However, there is still no consensus about a universal training regime for HFpEF patients and it may even be beneficial to combine exercise training with dietary interventions and pharmaceutical interventions to further improve exercise tolerance. Further research needs to clarify these aspects.


