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PHYSICAL ACTIVITY AND HEART FAILURE OF PRESERVED LEFT VENTRICULAR EJECTION FRACTION

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Abstract

Heart failure with preserved left ventricular ejection fraction (HFpEF) is a clinical syndrome in which the structure and the function of the heart are damaged, with stiffness of the heart muscle, increased pressures in diastole and in the pulmonary circulation. The latest understanding of HFpEF is that it is a systemic disease of the microcirculation with chronic inflammation and impaired cellular metabolism. The aim of this review was to determine the association between physical activity and HFpEF based on the available research. By summarizing the literature data, it was shown that a sedentary lifestyle represents a risk factor for HFpEF and that continuous physical activity prevents the occurrence of HFpEF, while in patients already suffering from HFpEF it increases functional capacity, as well as the quality of life, mainly due to the improvement of peripheral muscles oxidative metabolism. The impact of physical activity on improving the diastolic function of the heart in people with heart failure is still under research. Patients with HFpEF usually have poor exercise tolerance, thus an individualized prescription of physical activity is indicated in accordance with their capabilities, preferably a combination of aerobic training, strength exercises, balance and an adequate diet. The gold standard for the assessment of aerobic capacity is the cardiopulmonary exercise test, which allows the measurement of oxygen consumption, maximum heart rate, the first and the second anaerobic thresholds, parameters needed for dosing the intensity of physical exercise.

Key words: HFPEF / FUNCTIONAL CAPACITY / CARDIOPULMONARY EXERCISE TESTING / SEDENTARY LIFESTYLE / EXERCISE

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HEART FAILURE – A COMPLEX CLINICAL SYNDROME

Heart failure is a complex clinical syndrome that results from a disruption of the heart's structure and function and is manifested by symptoms such as fatigue and poor exercise tolerance, a feeling of shortness of breath, orthostatic dyspnea, and lower limb edema (McDonagh, 2021). The heart, being the central organ of circulation, has the function of collecting blood from the periphery, sending it to the lungs for oxygenation and re-pumping it to all other organ systems, enabling adequate distribution of oxygen and other necessary substances throughout the body (Verhoeff, 2017). Heart failure occurs when the heart does not have adequate pumping capacity or when it still has a relatively preserved contractile force, but the blood filling process in diastole is impaired (McDonagh, 2021, Pfeffer, 2019, Bourlaug, 20104). Heart failure affects more than 60 million people worldwide (5). The former classification into systolic and diastolic heart failure has been replaced by the one according to the ejection fraction of the heart's left ventricle (LV EF), which represents the percentage of blood pumped out during one heart cycle in relation to the volume of blood at the end of diastole. According to this classification, there is heart failure of reduced LV EF <40% (HFrEF - the abbreviation of heart failure with reduced EF), mildly reduced LV EF 40-49% (HFmrEF - the abbreviation of heart failure with mildly reduced EF) and preserved LVEF ≥ 50 %, (HFpEF – the abbreviation of heart failure with preserved EF) (McDonagh, 2021, Pfeffer, 2019, Borlaug, 2010).

For a long time, clinicians recognized and treated only HFrEF, while diastolic heart failure (HFmrEF and HFpEF) was a matter of discussion (Pfeffer,2019, Borlaug, 2010). In recent years, HFpEF has not only been recognized as a separate clinical entity but is currently in the center of attention for cardiologists around the world. The HFpEF incidence is apparently increasing - it used to be the less prevalent variant of heart failure, yet currently equals to HFrEF, and according to the latest epidemiological data its prevalence will reach up to 70% of the total heart failure population (Vasan, 2018, Savarese, 2022), considering the increasing prevalence of about 1% in relation to HFrEF per year (Borlaug, 2020).

PATHOPHYSIOLOGY OF HEART FAILURE WITH PERSERVED EJECTION FRACTION (HFpEF)

The understanding of HFpEF has changed over the decades of research. The scientific world travelled across a long way from understanding the classic simple model of diastolic dysfunction of the heart as a consequence of long-term hypertension that causes concentric remodeling and hypertrophy of the heart muscle, to indications that HFpEF is actually a disease of the microvasculature and cellular metabolism (Gevaert, 2022). It was noticed that the patients with this type of heart failure are phenotypically similar – they are more frequently older women, obese, who have arterial hypertension and atrial fibrillation (Pfeffer, 2019, Gevaert, 2022). As the typical HFpEF patient is an obese, dyspneic woman with poor exercise tolerance (Gevaert, 2022), the question arose whether this is an isolated heart disease or just a cardiac manifestation of systemic dysfunction characterized by increased body mass, systemic inflammation, and impaired microcirculation, related to physical inactivity and inadequate nutrition (Gevaert, 2022, Pandey, 2018, Pandey&Berry 2015). From the above said came the hypothesis that regular physical activity and a healthy diet can prevent this type of heart failure, but that these can also be treatment modalities, which will be discussed in more detail in the following text.

Pathophysiologically, what disrupts the phases of active and passive relaxation of the heart muscle in diastole is its stiffness, which is conditioned by changes in both the extracellular matrix, with the accumulation of collagenand changes in the cardiomyocytes and their contractile proteins (Pfeffer, 2019, Borlaug, 2010, Borlaug, 2011). A relationship was found between the degree of titin protein phosphorylation and cardiomyocyte elasticity (Borlaug, 2010). It has been proven that in metabolic syndrome there is a chronically elevated level of pro-inflammatory cytokines and oxidative stress (Paulus, 2020), that influence the expression of cellular signaling pathways, titin phosphorylation, and the accumulation of collagen in the intercellular space, all of which lead to increased heart muscle stiffness (Borlaug, 2010, Paulus, 2020). Sedentary lifestyle,

aging and obesity lead to chronic systemic inflammation, and physical activity has been shown to reduce the concentration of pro-inflammatory cytokines (Morawin, 2021, Papathanasiou, 2022, Hayashino, 2014).

Currently, taking everything into account, the criteria for making the diagnosis of HFpEF are the presence of symptoms of heart failure (difficulty breathing, reduced exercise tolerance) and LV EF ≥50% with increased LV filling pressure, and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest, i.e. ≥25 mmHg during exercise. (McDonagh, 2021, Borlaug, 2020)

HFpEF ANF REDUCED EXERTION TOLERANCE

Bearing in mind that HFpEF is a syndrome and is manifested by multiorgan dysfunction, the reduced effort tolerance of these individuals is influenced by cardiac and peripheral mechanisms (Guazzi 2022, Baratto, 2022, Nayor, 2020). The pressure in the LV does not have to be significantly high at rest, but during exertion hemodynamic insufficiency occurs due to impaired active and passive relaxation of the heart muscle, chronotropic incompetence, and reduced stroke volume - the LV filling pressure increases, it is retrogradely transmitted to the left atrium and pulmonary capillary bed (Borlaug, 2010, Borlaug, 2011, Paulus, 2020, 17 Guazzi 2022, Baratto, 2022, Nayor, 2020). Inadequate response to effort is also influenced by frequent atrial rhythm disturbances and the absence of left atrial function (Paulus, 2020, Guazzi, 2022, Nayor, 2020). Ventilation disorders and anemia, which are often associated with HFpEF, contribute to the reduced exercise capacity (Guazzi, 2022, Nayor, 2020). In one study that examined the influence of different hemodynamic parameters on exercise tolerance, Wolsk et al. identified three variables that were independently associated with reduced exercise tolerance in HFpEF. These are - PCWP, reduced LV stroke volume, and body mass index (Wolsk, 2019). In the recent years, there is a growing interest in and evidence about reduced perfusion and impaired oxidative metabolism of peripheral muscles in HFpEF patients (Upadhya, 2015, Adams, 2016). In the study published this year, Sarma et al. pharmacologically lowered PCWP and exposed study subjects to physical activity, but this intervention did not lead to better exercise tolerance (Sarma, 2023). It is well known that oxygen consumption depends both on the cardiac output and the peripheral utilization, i.e. the diffusion of oxygen between the peripheral microcirculation and the muscles (Guazzi, 2022). This was investigated by Houstis et al, and through a detailed analysis of cardiopulmonary testing parameters, the authors concluded that the dominant reason for reduced exercise tolerance in addition to reduced LV stroke volume is reduced peripheral diffusion (Houstis, 2018). The question arises - is HFpEF in fact a mitochondrial disease and what role does physical activity play in the pathophysiology and treatment of HFpEF?

PHYSICAL INACTIVITY AS A RISK FACTOR FOR HfpEF

Large observational studies have shown a causal relationship between a sedentary lifestyle and diastolic heart dysfunction (Brinker, 2014, Pandey&Allen 2017, Bhella, 2014). In their research, Brinker et al. recruited 1678 men and 1247 women and included them in a large epidemiological cohort of the Cooper Research Institute in Dallas, USA, where they underwent an echocardiographic examination in the period from 1999 to 2011 (Brinker, 2014). The subjects were divided into four groups according to the level of physical fitness, which was assesed by the Balke protocol on a treadmill. By analyzing the correlation between the echocardiographic parameters - the relative thickness of the LV wall, the volume of the left atrium, the end-diastolic diameter of the LV, LV EF, the diastolic mitral annular velocity and the level of physical fitness of the subjects, it was concluded that people with less physical condition had more often echocardiographic signs of diastolic dysfunction and concentric remodeling, which implied that these individuals had a higher risk of developing HFpEF later in life (Brinker, 2014). And indeed, Pandey et al. further analyzed the medical records of the before mentioned Cooper Institute study cohort and came to the conclusion that people who lived a sedentary lifestyle in middle age were much more likely to be hospitalized for heart failure later in life (Pandey&Patel, 2015). The authors calculated that an increase in physical activity by just one metabolic unit (MET as an abbreviation of Metabolic Equivalent of Task) reduces the risk of hospitalization due to heart

failure in the future by 17%. Importantly, physical activity was singled out as an independent risk factor regardless of other cardiovascular comorbidities, i.e. risk factors (Pandey&Patel, 2015). Similar results were obtained by analyzing the cardiorespiratory functional capacity and echocardiographic parameters of 2544 people aged 18 to 30 who were included in the CARDIA study (Coronary Artery Risk Development in Young Adults) (Pandey&Allen, 2017). A repeated cardiac ultrasound examination after 20 years of follow-up concluded that a low level of cardiorespiratory fitness, which was initially assessed by modified Balke protocol treadmill test and self-reported physical activity level, was associated with increased LV filling pressure, which is pathognomonic for HFpEF. These people also more frequently had impaired heart muscle contractility. However, a low level of physical fitness was an independent risk factor for the development of diastolic dysfunction, while its effect on the contractile ability of the heart was associated with the existence of other cardiovascular risk factors (Pandey&Allen, 2017). Bella et al. observed 102 healthy elderly individuals and showed that aging and a sedentary lifestyle led to increased stiffness of the heart muscle, but that regular exercise at least 4-5 times a week increases the compliance of the heart muscle (Bhella, 2014). A meta-analysis of more than 10 different cohort studies showed that the prevention of heart failure is dose dependent on the level of physical activity (Pandey&Garg, 2015, 30 Pandey&LaMonte, 2017), and that physical inactivity is an isolated risk factor for the development of HFpEF, but not HFrEF (Kraigher-Krainer, 2013).

PHYSICAL ACTIVITY AS A THERAPEUTIC MODALITY

In younger people, who live a sedentary lifestyle, physical activity can lead to desirable relaxation of the heart muscle (Howden, 2018). Hieda et al. showed that a year of intensive exercise, in asymptomatic middle-aged individuals with existing signs of LV hypertrophy and diastolic heart dysfunction, leads to a reduction in heart muscle stiffness and prevention of HFpEF (Hieda, 2021). The benefit of regular physical activity in the primary prevention of cardiovascular diseases is generally known and proven, but more research is focusing towards tosecondary prevention, treatment and cardiovascular rehabilitation (Arnett, 2019, Pelliccia, 2020).

Until recently, there were no pharmacological options for the treatment of HFpEF. According to the current recommendations for the treatment of heart failure of the European Society of Cardiology (McDonagh, 2021), physical activity is recommended for all patients with heart failure in accordance with their capabilities, in order to improve fitness, quality of life and reduce the number of hospitalizations due to heart failure (recommendation class I, level evidence A). Cardiovascular rehabilitation and physical activity should also be considered in individuals with advanced heart failure, comorbidities, and severely reduced exercise tolerance (recommendation class IIa, level of evidence C) (1). The HF-ACTION study showed that individually dosed physical activity is safe in people with heart failure (36). Randomized clinical trials conducted over the past 2 decades have shown unequivocally that physical activity increases aerobic capacity and, at least partially, quality of life in people with HFpEF (Alves, 2012, Angadi, 2012, Da Silveira, 2020, Edelmann, 2011, Fu, 2016, Gary, 2004, Haykowsky, 2012, Kitzman, 2010, Kitzman, 2013, Kitzman 2016, Smart, 201237-47). What is not clear is whether, as in people without heart failure, physical activity can induce reverse remodeling and improve diastolic heart function in people with HFpEF. In individual studies, conducted on a smaller number of subjects, an improvement in the morpho-functional characteristics of the heart was noted (Edelmann, 2011, Fu, 2016, Angadi, 2012, Da Silveira, 2020). Eldeman et al. showed that after 6 months of controlled exercise 3 times a week, which included 35 minutes of cycling and 35 minutes of strength training, there was an improvement in echocardiographic parameters of diastolic function - LV filling pressure [early LV filling velocity in diastole (E) /early annular mitral LV filling velocity (e')] and indexed left atrial volume (LAVI) (Edelmann, 2011). Other studies that analyzed the impact of different modalities and intensity of exercise on diastolic function, also showed their positive impact (Fu, 2016, Angadi, 2012, Da Silveira, 2020). A meta-analysis of these studies, however, has not yet found a statistically significant improvement in diastolic function parameters (Pandey&Parashar, 2015, Fukuta, 2019, Lin, 2022). Given that physical activity improves the functional and aerobic capacity of people with HFpEF, without significant impact on cardiac function, it

is assumed that there are other mechanisms through which exercise manifests its benefits. Haykowsky and the authors showed that in their study of 40 participants (of which 18 were controls), the greatest impact (84%) on the improvement of aerobic capacity (peak VO_2) had improved utilization, i.e. diffusion of oxygen in the periphery (a–vO_2diff – arteriovenous oxygen content difference) (Haykowsky, 2012). Physical activity leads to molecular and cellular changes in peripheral muscles that lead to increase in their oxidative potential (Adams, 2016, Winzer, 2022). It has been shown that certain exercise modalities (HIIT - high intensity interval training) in patients with HFpEF increase muscle energy metabolism (Bozkurt, 2021). The first large multicenter study comparing different exercise modalities in people with HFpEF, OptimEX-Clin, was completed in 2018 (Mueller, 2021). The study was conducted in 5 centers in Germany, Belgium and Norway and included 120 women and 60 men with stable HFpEF, mean age 70 years and BMI 30 kg/m^2, NYHA II. The participants were randomized into three groups: 1) 58 were in the HIIT program – 3 times a week for 38 minutes (4 minutes of intense activity with 3 minutes of rest in between); 2) 58 were in the program of moderate continuous aerobic training (MCT) - 5 times a week for 40 minutes; and 3) 60 subjects were controls who were advised physical activity according to current recommendations. After three months of exercise under the supervision of the researcher, the study continued for another 9 months without direct supervision. After 3 months, there was an improvement in aerobic capacity in patients who performed HIIT and MCT (VO_2 increased by 1.0 mL/kg/min after HIIT and 1.6 mL/kg/min after MCT, and in the control group only by 0.6 mL/kg/min). No statistically significant difference was observed between different exercise modalities, although in previously conducted smaller randomized clinical trials, HIIT showed superiority (Angadi, 2012, Da Silveira, 2020, Siddiqi, 2023). Namely, it is known that the greater the intensity of exercise, the greater the prevention of cardiovascular risk in healthy people (Schnohr, 2011). It has been shown that high-intensity interval exercise leads to an increased accumulation of metabolites, ions and free radicals in muscles that trigger cellular signaling pathways, which affect the expression of specific gene loci, all of which increase mitochondrial oxidative capacity and oxygen utilization (Hansen, 2021, MacInnis, 2016). The effect of exercise on peripheral circulation and endothelial function is the subject of current and future research. In a secondary analysis of the OptimEx study, Gevaert et al. showed that although indicators of arterial stiffness were impaired in individuals with HFpEF, endothelial function was not significantly impaired. In their analysis, a one-year exercise program (HIIT and MCT) did not improve peripheral arterial and endothelial function (Gevaert, 2023).

CARDIOPULMONARY TEST AND HFpEF

The gold standard for assessing physical fitness or the total functional capacity of the organism, is the cardiopulmonary stress testing (Guazzi, 2017). During this testing, subjects are exposed to progressive effort on a treadmill or bicycle, with simultaneous analysis of blood pressure, electrocardiogram (ECG) and concentration of gases in exhaled air measured through a mask on the face. The occurrence of possible symptoms is also monitored (Guazzi, 2012, Guazzi, 2017). The cardiopulmonary exercise testng anables the evaluation of the cardiac and pulmonary function, as well as the peripheral muscles and mitochondria. The most important parameter used to assess physical condition, i.e. functional capacity, is peak VO_2. According to Fick's principle, VO_2 depends both on cardiac output and peripheral oxygen utilization ($VO_2 = Q \times [CaO_2 – CvO_2]$) (Guazzi, 2012, Guazzi, 2017). For each person, there is a predicted maximal VO_2, (VO_2 max), which is calculated based on age and gender. During the cardiopulmonary exercise testing, the functional capacity is assessed by the percentage of the predicted maximal VO_2 that has been achieved. If the VO_2 peak achieved during the testing is less than 80% of the age and gender predicted VO_2 max, or less than 15-20 mL/min/kg, it is considered that the aerobic capacity is reduced (Guazzi, 2012, Guazzi, 2017). People suffering from HFpEF have a very reduced effort tolerance, their average peak VO_2 is about 15 mL/min/kg, which means that they need about 60% of their total strength for daily activities, such as dressing up, about 70% for slow walking, and that they are often functionally dependent on other persons (Nayor, 2020). Based on the other evaluated parameters, one can gain an insight into whether the cause of fatigue is of central or peripheral origin, whether

it is mainly caused by heart or lung dysfunction, or is the problem in the peripheral utilization of oxygen (Guazzi, 2012, Guazzi, 2017).

EXERCISE PRESCRIPTION AS THERAPY FOR HFpEF

Exercise prescription for people suffering from heart failure must be carried out with great caution and in a way that implies an adequate evaluation of the existing cardiorespiratory status (Hansen, 2021, Sachdev, 2023, Mezzani, 2012). The initial evaluation of a person's cardiorespiratory status and condition is carried out with a cardiopulmonary stress test (Guazzi, 2022, Hansen, 2021, Mezzani, 2012). Alternatively, with much less precision, a simple exercise test can be used to assess fitness, without measuring the concentration of gases in exhaled air (Fletcher, 2013). By 6ssessing parameters such as peak VO_2, maximum heart rate, first and second ventilatory thresholds (VT1 and VT2), the cardiopulmonary test enables adequate dosing and planning of exercise programs (Binder, 2008, Cavigli, 2020, D'Ascenzi, 2022). The maximum heart rate (HR max) is the parameter based on which physical activity was traditionally prescribed, however, the cardiopulmonary test allows for an even more accurate assessment of both the existing functional capacity and the one that should be reached. Moreover, the intensity of exercise is determined by the percentage of estimated peak VO_2 that should be achieved during exercise, and VT1 and VT2 help in this process. VT1 or first lactate threshold, represents the moment when the body has exhausted its existing aerobic capacity, cells switch to anaerobic metabolism, in which the glucose molecule is reduced to lactate, and then, the lowering of blood pH leads to an increase in minute ventilation (VE). In a cardiopulmonary exercise test, VT1 can be recognized as an increase in the slope of the curve relating VE to carbon dioxide production (VCO2). This occurs at about 50-60% of peak VO_2. When compensatory ventilatory buffers are exhausted, there is a re-increase in blood lactate and a drop in pH, and this moment is called VT 2. It usually occurs at 70-80% of maximal aerobic capacity (Binder, 2008, Cavigli, 2020, D'Ascenzi, 2022). Based on these parameters, exercise of the desired intensity can be prescribed:

1) light physical activity means that VT1 is not reached, which is an intensity of less than 40% of the peak VO_2 or 55% of the HR max;
2) moderate intensity of physical activity is at 40-69% of the VO_2 peak or 55-74% of the HR max;
3) intense physical activity at 70-85% of the peak VO_2 and 75-90% of the HR max;
4) very intense physical activity implies that VT2 has also been reached, i.e. intensity greater than 85% of the peak VO_2 and 90% of the HR max (Pelliccia, 2020).

Although HR max is easier to estimate, it is more appropriate to dose physical activity using VO_2, VT1 and VT2, because HR max is influenced by pharmacological therapy used to treat HFpEF comorbidities (D'Ascenzi, 2022).

Exercise prescription means determining the intensity, duration of exercise, number of sessions during the week, type of exercises (Hansen, 2021, Mezzani, 2012). According to the 2020 Recommendations of the European Association of Cardiologists for Sports Cardiology and Physical Activity of People Suffering from Cardiovascular Diseases, aerobic physical activity at 40-80% of the peak VO_2, lasting 20-60 minutes, 3-5 times a week is recommended for people with chronic heart failure, continuously or in intervals, in combination with daily balance training and strength training 2-3 times a week (10-15 repetitions of 8-10 different exercises with an intensity of 40-60% of the maximum voluntary contraction), with a progressive increase in the volume of activity at regular controls of the prescribing physician every 3-6 months. For patients with HFpEF, it is recommended to start with 10 minutes of aerobic training and 10 minutes of strength training, to reach at least 30-45 minutes of physical activity three or more times a week in the next month. A change in lifestyle and other risk factors is also advised (recommendation class I, level of evidence C) (Pelliccia, 2020). So far, there are no reliable data on whether HIIT is superior to MCT (Mueller, 2021, Siddiqi, 2023) in people with HFpEF, but introduction of regular physical activity according to their capabilities is absolutely indicated (McDonagh, 2021, Pelliccia, 2020, Sachdev, 2023). Combining aerobic training, strength exercises and diet gives the best results (Kitzman, 2016, Brubaker, 2022). Strength exercises are of great importance for patients with HFpEF

and can improve their functionality and quality of life - in smaller studies it has been shown that isolated exercise of peripheral muscles, knee extension, improves blood flow in m. quadriceps and a person's functional capacity (Esposito, 2011, Hearon, 2022). New methods such as respiratory musculature exercises and electrical muscle stimulation also give good results (Zhuang, 2021). Kitzman and the authors emphasized the importance of prompt initiation of rehabilitation, still during hospitalization after acute episodes of heart failure, with a focus on mobility, balance, gait and strength exercises (Kitzman, 2021).

CONCLUSION

Insufficient physical activity is a risk factor for the development of HFpEF, through complex pathophysiological mechanisms associated with obesity, chronic inflammation, and impaired microcirculation. Continuous programmed and free physical activity prevents the occurrence of HFpEF. In HFpEF patients it increases functional capacity and quality of life, mainly due to the improvement of the oxidative metabolism of peripheral muscles. The effect on improving the diastolic function of the heart is still the subject of research. Individualized prescription of exercise is recommended for patients with HFpEF in accordance with their capabilities and effort tolerance. A combination of aerobic, strength, balance training and adequate diet gives the best results.

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