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HEART FAILURE THERAPY CHALLENGES IN OBESE PATIENTS

Abstract: Obesity is one of the most significant independent risk factor for developing heart failure (HF) through direct and indirect mechanisms. Excessive secretion of aldosterone and activation of the renin-angiotensin system (RAAS) in obese patients leads to sodium retention and an increase in extracellular volume, which contributes to the development of heart failure and increased cardiovascular risk. Abdominal visceral obesity is associated not only with an increased risk for the development of heart failure with preserved ejection fraction (HFpEF), but also with a high risk for the development of diabetes mellitus and hypertension in both sexes, but more dominantly in women, with an increase in incidence with menopause. Multiple studies and meta-analyses have confirmed that obese patients with heart failure regardless of ejection fraction (HFpEF and HFrEF) have better survival compared to those of normal or underweight, a phenomenon known as the obesity paradox. The HF-ACTION trial showed that even small improvements in cardiorespiratory fitness could lead to significant improvements in cardiovascular outcomes, reducing the impact of the obesity paradox on the clinical outcome of heart failure. The ESC recommendations for heart failure advise weight loss in order to prevent cardiovascular disease in obese and overweight patients, and gradual weight loss should be considered in patients with heart failure and BMI > 35 kg/m^2, while in patients with heart failure and BMI<35 kg/m^2, weight loss is not recommended. The goal of bariatric procedures is to prevent or delay the onset of heart failure, not only by reducing body weight but also by reducing risk factors. The randomized DAPA-HF trial showed that the use of dapagliflozin proved to reduce the composite outcome of worsening heart failure or cardiovascular death in heart failure patients with BMI>30 kg/m^2 and in HF patients with BMI<30 kg/m^2. The EMPEROR-preserved and DELIVER trials showed that therapy with SGLT2 inhibitors in patients with HFpEF and BMI>30kg/m^2 reduces the risk of hospitalization and cardiovascular death. It is recommended that patients in the terminal stage of heart

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failure in the pre-transplantation period and placed on the list for heart transplantation achieve target values of BMI<30 kg/m^2 in order to achieve a better clinical outcome and reduce mortality after transplantation.

Keywords: obesity, heart failure, the obesity paradox, cardiorespiratory fitness, bariatric surgery, SGLT2 inhibitors.

Obesity is one of the most significant independent risk factors for the development of heart failure (HF). Various forms of cardiovascular diseases and risk factors for the development of cardiovascular diseases are associated with obesity (hypertension, coronary artery disease, atrial fibrillation, metabolic syndrome, diabetes, dyslipidemia, systemic inflammation, obstructive sleep apnea), which contributes to the development of heart failure (1). About 29-40% of heart failure patients are overweight, and 30-49% are obese. Overweight and obese are associated with a significantly higher prevalence of heart failure with preserved ejection fraction (HFpEF) than heart failure with reduced ejection fraction (HFrEF), and more than 80% of patients with HFpEF are overweight or obese (2,3). The Framingham Heart Study, which included 5881 patients, showed an increase in the prevalence of heart failure by 5% in men and by 7% in women for every 1 kg/m^2 increase in BMI (4). Obesity is associated with a significantly increased risk of cardiovascular morbidity and mortality and there is a significant association between BMI and heart failure with a five-fold increase in the incidence of heart failure in the morbidly obese (BMI ≥35 kg/m2) compared to those of normal weight (BMI between 18.5 kg/m2 and 24.9 kg/m2). The risk of developing heart failure progressively decreases with increasing cardiorespiratory fitness (CRF) in all types of obesity, independent of BMI, and there is a significantly greater impact of cardiorespiratory fitness compared to BMI for the development of heart failure (5,6).

The increased amount of adipose tissue leads to hyperdynamic circulation, systemic vasodilatation, increased blood volume and cardiac output, increased stress of the left ventricular wall, concentric hypertrophy and remodelling, and later left ventricular dilatation and right ventricular dilatation. The heart rate is unchanged or slightly increased, but the stroke volume increases proportionally with the increase in body weight (7).

Excessive secretion of aldosterone and activation of the renin-angiotensin system (RAAS) in obese patients leads to sodium retention and an increase in extracellular volume, which contributes to the development of heart failure and increased cardiovascular risk. The increase in aldosterone originates not only from the activation of the RAAS system in the adrenal gland but also from the increased secretion of aldosterone from adipocytes (8). Hyperplasia and hypertrophy of adipocytes lead to an increased expression of neprilysin on the surface of adipocytes and an increased concentration of soluble neprilysin in the plasma, which explains the lower concentration of natriuretic peptides (BNP) in the plasma of obese people, including those

with heart failure, which makes it difficult to diagnose heart failure before the development of dyspnea and oedema (9). Increased secretion of leptin from adipocytes leads to sodium retention by direct action on the renal tubules and increased activity of the sympathetic nervous system and other neurohumoral mechanisms on kidneys. Sodium retention leads to increased blood volume in the obese, which leads to the development of hypertension and ventricular hypertrophy and dilatation. Obesity also leads to increased left ventricular filling pressure at rest and during exercise and left atrial enlargement, which leads to reduced exercise tolerance (10). Visceral obesity is associated with systemic inflammation and increased secretion of pro-inflammatory cytokines from adipocytes (TNF-alpha, IL-1, IL-6), which leads to cardiomyocyte fibrosis and microvascular circulation disorders (11). An increase in epicardial adipose tissue and paracrine secretion of adipokines and cytokines leads to a prolonged pro-inflammatory state that, combined with visceral obesity, contributes to the fact that smaller increases in plasma volume lead to a significant increase in left ventricular filling pressure, cardiac fibrosis and the development of HFpEF and arrhythmias (atrial fibrillation). Visceral obesity is associated with the development of insulin resistance, and the state of hyperinsulinemia leads to the activation of the RAAS and the sympathetic nervous system, disorders of myocardial metabolism, reducing the utilization and oxidation of glucose, and increased oxidation of free fatty acids (FFA), which are increasingly released from adipose tissue, which leads to cardiomyocyte oxidative stress, mitochondrial dysfunction, apoptosis and reduced cardiomyocyte contractility (12,13). Abdominal visceral obesity is associated not only with an increased risk for the development of HFpEF, but also with a high risk for the development of diabetes mellitus (DM) and hypertension in both sexes, but more dominantly in women, with an increase in incidence with menopause (14).

Multiple trials and meta-analyses have confirmed that obese patients with heart failure (HFpEF and HFrEF) have better survival compared to those with normal or lower body weight, a phenomenon known as the obesity paradox. This phenomenon is more pronounced in elderly patients with type I obesity (BMI between 30 kg/m^2 and 34.9 kg/m^2) compared to patients with a BMI greater than 35 kg/m^2, where the cardioprotective role of higher body mass has less influence (15). Cardiovascular mortality, all-cause mortality, and rehospitalization due to worsening heart failure (HF) are higher in patients with lower BMI, and the risk decreases with increasing BMI. For every 1% increase in body fat, the incidence of major cardiovascular events decreases by 13%. One trial involving 108927 patients with decompensated HF showed a 10% reduction in mortality for each five-unit increase in BMI (16). Advanced heart failure is a catabolic state leading to cachexia and overweight patients have a greater metabolic reserve. Adipose tissue has an increased expression of TNF-alpha receptors, which has a protective role in obese patients by neutralizing TNF-alpha from the circulation, as one of the most important pro-inflammatory cytokines. Obese patients with heart

failure have reduced expression of circulating natriuretic peptides, which leads to the earlier manifestation of HF symptoms (oedema and dyspnea) in less advanced stages of HF, which leads to earlier initiation of cardioprotective therapy and better prognosis of HF patients. Obesity is commonly associated with increased blood volume and higher blood pressure and obese patients with HF have better tolerance to high doses of cardioprotective drugs. A higher BMI in patients with heart failure is associated with greater muscle mass and strength and greater cardiorespiratory fitness, which significantly improves the prognosis of heart failure (17).

Cardiorespiratory fitness (CRF) represents the maximum amount of oxygen uptake that is transported and consumed by the working tissue ("peak exercise oxygen uptake" - peak VO_2) during a cardiopulmonary exercise test (treadmill test). Low CRF is associated with a statistically significant increase in cardiovascular mortality in both sexes, and low CRF is a more significant prognostic factor for mortality than other traditional cardiovascular risk factors. Low levels of physical activity and low CRF lead to faster development of risk factors (hypertension, diabetes mellitus, coronary artery disease) that lead to heart failure, and even the absence of risk factors with a sedentary lifestyle leads to increased stiffness of the left ventricle and development HF. A moderate or higher level of physical activity is associated with a reduction in the risk of developing HF in both sexes independent of BMI and for each increase of 1 MET (1 MET = 3.5 ml 0_2/kg/min) the risk of developing HF decreases by 16%. CRF significantly reduces the influence of BMI on HF prognosis (18). Trials have shown that the obesity paradox does not persist in patients who have a relatively preserved CRF (peak VO_2 > 14 ml/kg/min) and the protective influence of a higher BMI is lost, and the role of CRF in the prognosis of HF becomes more significant. In one trial that included 2066 patients with systolic heart failure (HFrEF), higher BMI had an impact on HF prognosis in patients with low CRF (peak VO_2 < 14 ml/kg/min). In patients with higher CRF (peak VO_2 > 14 ml/kg/min), the effect of BMI on survival in HF patients is lost (19). The HF-ACTION trial showed that even small improvements in CRF can lead to a significant improvement on cardiovascular outcomes - reducing the risk of overall mortality and hospitalization. This trial confirmed not only the safety but also the significant clinical benefit of physical training in HFrEF and confirmed the Class I recommendations of the ACC/AHA and European (ESC) guidelines for the treatment of heart failure that exercise and physical activity is safe and effective in patients with heart failure and improves functional status and prognosis (20).

Intentional weight loss in obese patients can improve hemodynamics, reduce circulating fluid volume and stroke volume, and reduce preload and afterload, which reduces the incidence of heart failure (HF). There is clear evidence that unintentional weight loss has a detrimental effect on patients with chronic heart failure (21). A loss of more than 5% of body weight in HF patients without oedema leads to a worse prognosis. A recent meta-analysis of 8 trials including 226506 patients with chronic

HF showed that weight loss > 5% was associated with a 74% higher risk of mortality compared to patients with stable body weight. Controlled reduction of body weight and increase of CRF in obese patients improves symptoms and functional capacity of HF patients. In patients with chronic stable HF, a gradual weight gain of up to 5% is associated with a better prognosis, and mortality increases moderately with excessive body weight loss of more than 5% (22). ESC recommendations for HF advise weight loss in order to prevent cardiovascular diseases in obese and overweight patients, and in patients with heart failure and BMI > 35 kg/m^2 gradual weight loss should be considered, while in patients with heart failure and BMI < 35 kg/m^2, weight loss is not recommended (21,22). When planning the diet of patients with HF, it is advised to restrict intake to 400 kcal/day with a diet plan that includes fruits and vegetables and polyunsaturated fatty acids and with planned aerobic activity leads to a potential improvement of CRF and a better outcome of patients with HFpEF (23,24,25, 26).

Bariatric procedures as a surgical treatment of obesity are recommended to reduce the incidence of heart failure and reduce cardiovascular mortality in patients with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with and 1 or more obesity-related co-morbidities. The goal of bariatric procedures is to prevent or delay the onset of heart failure not only by reducing body weight but also by reducing risk factors for the development of HF such as hypertension, DM and dyslipidemia and reducing the incidence of cardiovascular events. By reducing the hemodynamic overload, there is a regression of left ventricular hypertrophy and improvement in diastolic dysfunction, reduction in the incidence of atrial fibrillation and sleep apnea syndrome, and improvement in cardiorespiratory fitness (27). The SOS (Swedish Obese Subjects) cohort trial followed the effect of bariatric procedures in men with a BMI >34 kg/m^2 and in women with a BMI >38 kg/m^2. This trial showed that weight loss achieved through bariatric procedures reduced cardiovascular morbidity and mortality in obese patients and reduced the risk of developing HF by 35% compared to a control group without bariatric procedures (28). Long-term follow-up of patients (for 15-20 years) showed a significantly lower number of hospitalizations and medication use after bariatric procedures. A retrospective study that included 21 heart failure patients who underwent bariatric procedures during 12 months of follow-up showed a significant weight loss - an average of 26 kg and a significant improvement in left ventricular EF (10 +/- 1.9 %) and a significant reduction in NYHA class - improvement of heart failure symptoms (29).

Beta-blockers, renin-angiotensin system (RAS) antagonists - ACI inhibitors and angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) represent the mainstay of heart failure therapy with reduced ejection fraction (HFrEF). RAS antagonists and beta blockers have been shown to prevent weight loss and/or lead to weight gain (30,31). In the COPERNICUS trial, which included 2289 patients with advanced HFrEF, it was shown that carvedilol prevents weight loss in

patients with a higher BMI, and affects weight gain in patients with a lower BMI. Beta-blockers reduce the activation of the sympathetic nervous system, which plays an important role in the development of cardiac cachexia in advanced heart failure (32). The SOLVD and Val-HeFT II trials showed an approximately 20% lower risk of significant weight loss (>6%) in patients treated with RAS antagonists (31). An effective HF therapeutic approach leads to improved hemodynamics and cardiac function, which facilitates physical activity and leads to increased weight and muscle mass and increases cardiorespiratory fitness. Mineralocorticoid receptor antagonists have a neutral effect on body weight (33). A retrospective observational study that followed the effects of sacubitril/valsartan (ARNI) in patients with HFrEF showed no effect of the drug on body weight during a 12-month follow-up (34). SGLT2 inhibitors (dapagliflozin and empagliflozin) have a moderate effect on body weight loss (average 1-3 kg) in randomized studies that followed patients with diabetes mellitus or heart failure (35). These drugs increase glycosuria and affect the loss of 50-100g of glucose per day, which leads to a daily caloric deficit and thus explains the effect of SGLT2 inhibitors on reducing body weight. The randomized DAPA-HF trial showed that the administration of dapagliflozin proved to reduce the composite outcome of worsening heart failure or cardiovascular death in HF patients with a BMI>30 kg/m^2 and in HF patients with a BMI<30 kg/m^2. During the eight-month follow-up of patients in the DAPA-HF trial, the average weight loss was about 1 kg, and this weight loss is considered safe in patients with HFrEF (36). SGLT2 inhibitors improve cardiorespiratory fitness (CRF), which is a strong risk factor for clinical outcomes in patients with heart failure (37). So far, there is no clear evidence of how the new class of drugs in HFrEF therapy - vericiguat (guanylate cyclase stimulator) and omecamtiv mecarbil (myosin activator) - affect body weight.

Obesity paradoxically protects patients with heart failure with preserved ejection fraction (HFpEF) from poor cardiovascular outcomes, although overweight is a significant risk factor for the devolopment of HFpEF. The risk of developing HFpEF increases by 34% for every 1 standard deviation increase in BMI, and weight loss can reduce the risk of developing HFpEF. Weight loss through lifestyle changes including diet, exercise, pharmacotherapy, and bariatric surgery is advised. A Mediterranean low-carbohydrate diet and aerobic training significantly reduce visceral and epicardial fat depots, which leads to a reduction in left ventricular mass and inflammatory cytokines, increases cardiorespiratory fitness and improves the quality of life in obese patients with HFpEF and reduces the risk of HFpEF occurrence (38). Mineralocorticoid receptor antagonists (MRAs) may have a significant benefit in obese patients with HFpEF. However, in the TOPCAT trial, treatment with spironolactone did not show a significant effect on reducing hospitalization, cardiovascular death and sudden cardiac death in patients with EF>50% and BMI≥31 kg/m2. Post hoc analysis of this study showed that patients with a lower level of NTproBNP in the

circulation, which correlates with the amount of visceral adipose tissue, could have a more significant benefit from MRA therapy (39,40). In the PARAGON-HF trial, the treatment of HFpEF with an angiotensin receptor antagonist/neprilysin inhibitor (sacubitril valsartan) showed that there was a trend towards a reduction in hospitalizations and cardiovascular death in patients with EF>45%, but the difference was not statistically significant compared to valsartan therapy (41). Statins reduce systemic inflammation, which is strongly associated with the pathogenesis of HFpEF in obese patients, but their clinical benefit in the treatment of HFpEF has not been confirmed in randomized clinical trials (42). The EMPEROR-preserved and DELIVER trials showed that therapy with SGLT2 inhibitors in patients with HFpEF and BMI > 30kg/m^2 reduces the risk of hospitalization and cardiovascular death. SGLT2 inhibitors modulate 2 important pathophysiological mechanisms of HFpEF in obese patients - sodium retention and systemic inflammation - through hemodynamic and metabolic pathways. Natriuresis achieved by the use of SGLT2 inhibitors leads to a decrease in plasma volume (reduction of about 7%) and a decrease in blood pressure (on average about 4/2 mm Hg systolic/diastolic values) which leads to a decrease in preload and afterload (43). SGLT2 inhibitors induce glycosuria associated with a negative caloric balance and urinary excretion of 200-250 kcal/day and reduce body weight (on average 2-3 kg) associated with a reduction of body fat and extracellular fluid, without affecting muscle mass leading to an increase in cardiorespiratory fitness (CRF) and a better prognosis in patients with HFpEF(44).

Obesity is associated with increased mortality after heart transplantation and patients with BMI>35 kg/m^2 in the period before heart transplantation have a worse cardiovascular outcome after transplantation. Obese patients after heart transplantation have a high degree of acute organ rejection and a higher five-year mortality compared to patients with normal weight or overweight (BMI<30 kg/m^2). It is recommended that patients in the terminal stage of heart failure in the pre-transplantation period and being placed on the list for transplantation achieve target values of BMI<30 kg/m^2 (45) Severe obesity (obesity class III) with BMI≥40 kg/m^2 is a contraindication for heart transplantation and it is recommended to achieve target values of BMI<30 kg/m^2 with diet, physical activity and bariatric procedures in order to achieve an optimal outcome after heart transplantation (46).

Conclusions

Obesity is associated with the occurrence of heart failure through direct and indirect mechanisms, and weight loss is associated with a reduction in the incidence of heart failure. In obese patients with heart failure, better survival has been proven and there is a significant benefit of higher body weight in patients with heart failure and BMI<35kg/m^2 in both sexes and in acute and chronic heart failure independent

of ejection fraction (HFpEF and HFrEF). Lifestyle modification – diet and aerobic physical activity with moderate weight loss lead to a reduction in cardiovascular risk and overall mortality. Even smaller increases in cardiorespiratory fitness (CRF) lead to significant improvements in cardiovascular outcomes, reducing the impact of the obesity paradox on the clinical outcome of heart failure. Bariatric surgery leads to a significant reduction in body weight, reduction of risk factors that influence the development of heart failure, and improvement of heart failure symptoms. Greater weight loss (more than 5%) is associated with a worse prognosis in patients with heart failure, and weight loss during SGLT2 inhibitor therapy in both HFrEF and HFpEF is safe and leads to a reduction in the risk of hospitalization and cardiovascular death. Heart transplantation in patients with BMI > 40 kg/m^2 is contraindicated and body weight reduction is advised with target values of BMI<30 kg/m^2 in order to achieve a better clinical outcome and reduce mortality after transplantation.

There is no conflict of interest.

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