HEART FAILURE WITH PRESERVED EJECTION FRACTION: THERAPEUTIC ENIGMA

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Abstract: *Heart failure with preserved ejection fraction (HFPEF) is increasing in prevalence with the aging of the population, and morbidity and mortality rates are comparable to that of heart failure with reduced ejection fraction (HFREF). Recent literature focusing on the pathophysiology underlying this disease suggests that multiple mechanisms are involved in the generation of the phenotype, such as abnormal relaxation and ventricular-vascular coupling, chronotropic incompetence, volume overload and endothelial dysfunction. Currently, no clinically proven treatments are shown to decrease morbidity and mortality in this population; however, there may be a novel multidisciplinary and multistage treatment strategy that can be studied to address this complex disease which incorporates pharmacologic and non-pharmacologic therapeutics. The treatment of patients with heart failure and preserved left ventricular (LV) function is not well established and remains mostly empirical. The lack of large placebo-controlled trials in this field seems to be due to the fact that investigators mainly focus on systolic dysfunction, which was for a long while perceived as the only causative mechanism of heart failure, and also because of the ambiguity of the definition of diastolic heart failure (DHF).*

Cuvinte cheie: *insuficiență cardiacă, insuficiență cardiacă diastolică, insuficiență cardiacă cu fracție de ejecție păstrată, insuficiență cardiacă cu fracție de ejecție redusă, tratamentul insuficienței cardiace*

Rezumat: *Prevalența insuficienței cardiace cu fracție de ejecție păstrată (ICFEp) este în creștere odată cu îmbătrânirea populației, iar ratele morbidității și mortalității sunt comparabile cu cele ale insuficienței cardiace cu fracție de ejecție redusă (ICFEr). Literatura recentă pune accent pe fiziopatologia care stă la baza acestei boli și sugerează faptul că multe mecanisme sunt implicate în generarea fenotipului, cum ar fi relaxarea anormală și cuplarea ventriculo-vasculară, incompetența cronotropică, suprasarcină de volum, redistribuirea și / sau disfuncția endotelială. În prezent, nu există tratamente dovedite clinic a fi capabile de a scădea morbiditatea și mortalitatea la această populație; cu toate acestea, se poate să existe o strategie nouă de tratament multidisciplinar și pe mai multe trepte, care poate fi studiată pentru a aborda această boală complexă care încorporează terapii farmacologice și nefarmacologice. Tratamentul pacienților cu insuficiență cardiacă și cu funcția ventriculară stângă (VS) păstrată nu este bine stabilit și rămâne în mare parte empiric. Lipsa studiilor mari, controlate placebo în acest domeniu pare a se datora faptului că anchetatorii se concentrează în principal asupra disfuncției sistolice, care a fost pentru multă vreme percepută ca singurul mecanism cauzal al insuficienței cardiace, și, de asemenea, din cauza ambiguității definiției insuficienței cardiace diastolice.*

HFPFE constitutes nearly half of all HF patients and IT is associated with high morbidity and mortality.(1) This phenotype is the predominant form of HF among the elderly, in women, and in those with a history of hypertension or diabetes. HFPEF patients have concentric left ventricular (LV) remodelling with a normal LV end diastolic volume, abnormalities of active relaxation, and increased passive ventricular stiffness.(2–3) In many studies, the effects of angiotensin-converting enzyme (ACE) inhibitors (4), β-blockers (5), and angiotensin receptor blockers (ARBs) have been assessed in HFREF, but few studies specifically evaluated the same compounds in HFPEF patients. Pharmacologic treatment of HFPEF patients is aimed to decrease blood pressure, promote regression of LV hypertrophy, prevent tachycardia, treat symptoms of congestion, and maintain atrial contraction.(6) Additionally, nonpharmacologic interventions, such as diet and physical exercise have proven their efficiency in early, small clinical investigations**.** The identification of the factors responsible for HFPEF is crucial for the therapeutic process as only a small proportion of the patients with symptoms of heart failure and preserved LV function have no identifiable underlying cardiac pathology.(7) Diseases that are known to impair diastolic function include hypertension, coronary artery disease, diabetes, obesity, aortic stenosis, atrial fibrillation, hypertrophic obstructive and nonobstructive cardiomyopathy, and restrictive cardiomyopathies (e.g., amyloidosis, sarcoidosis, and hemochromatosis).(8)

Diet and lifestyle

The identification and treatment of other associated co-morbidities that directly or indirectly worsen the diastolic function, such as high blood pressure, diabetes, and hypercholesterolemia, are important in reducing the risk of subsequent HFPEF.(9,10) PhaWeight loss: exercise helps to achieve and maintain a healthy weight and control diabetes,

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elevated cholesterol, and high blood pressure.(10)

Randomized clinical trials with low-salt and fluid-restricted diet showed that following a 6-month period of an individually prescribed salt- and fluid restricted diet, patients with mild to moderate HF showed clinical improvements with an absence of edema and fatigue, leading to an improvement in New York Heart Association (NYHA) class and quality of life.(10)

Smoking cessation: smoking is a major risk factor for HF. No prospective studies have assessed the effects of smoking cessation in patients with HF. Observational data support the association between continued smoking and increased HF mortality and rates of hospitalizations as compared to non-smokers, recent ex-smokers, and longer ex-smokers.(11,12) Alcohol may have a negative inotropic effect, and may be associated with an increase in blood pressure.(11) Alcohol intake should be limited to 10 to 20 g/d (1–2 glasses of wine/day).

Pharmacologic treatment

- **HF trials in HFPFE**

No pharmacologic therapy was demonstrated to reduce mortality and morbidity in HFPEF patients. In many large, randomized, controlled clinical trials, researchers have assessed the beneficial effects of ACE inhibitors, β-blockers, and ARBs in HFREF patients, but these effects have not been established in HFPEF patients.

Two large-scale HFNEF trials have reported their disappointing results: in the CHARM Preserved trial, the ARB candesartan produced a modest reduction in hospitalizations for HF but had no effect on mortality (13); in PEP-CHF, the ACE-inhibitor perindopril had similar effects.(14)

The I-PRESERVE trial assigned HFNEF patients to irbesartan or placebo and demonstrated no decrease in mortality or hospitalizations for cardiovascular causes.(14)

Two other studies showed a positive effect of enalapril on the symptomatic improvement of patients with HFPEF. One was conducted with a group of elderly patients with prior myocardial infarction, and one was a subanalysis of the Vasodilator in Heart Failure Trials. On the contrary, no positive effect of enalapril was shown in the subanalysis of 50 patients in the Consensus trial.(13)

Aldosterone antagonists reduce myocardial fibrosis.(15) In addition, aldosterone antagonists lower blood pressure and directly affect myocardial relaxation, which is also useful in the treatment of diastolic LV dysfunction in HFNEF patients. In the ongoing trials Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) and Aldosterone in Diastolic HF (ALDO-DHF), the role of spironolactone versus placebo is being studied to elucidate if an anti-fibrotic intervention strategy is adequate to improve the outcome in HFNEF.(15)

The reduction in heart rate and prevention of tachycardia with β-blocker treatment has several benefits on diastolic function, including a prolongation of diastole and the LV filling time and an improvement of ischemia. In addition, β-blockers have demonstrated benefits in reducing blood pressure and myocardial ischemia, promoting regression of LV hypertrophy, and antagonizing the excessive adrenergic stimulation during HF. β-blockers have been associated with decreased HF symptoms in HFPEF patients.(16) The study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure (SENIORS) trial should be mentioned as it is the first large HF outcome trial restricted to a population over 70 years of age and as it specifically looked at a subgroup of patients with a LVEF >35%.(17) The SENIORS trial showed that treatment with the β-blocker nebivolol decreased cardiovascular morbidity and that this effect did not differ between patients with a LVEF < 35% and a LVEF >35%. Favourable effects of nebivolol treatment on LV remodelling such as a decrease in LV end-systolic volume and an increase in LVEF were however limited to patients presenting with a LVEF > 35%. Beneficial effects of β-blocker treatment in older HF patients are in line with previous trials on the use of β-blockers in HF such as the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (patients ≥65 years) (18), the Cardiac Insufficiency Bisoprolol Study (CIBIS II) trial (patients ≥71 years) (19), and the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) trial (patients > 69 years) (20), which all showed a reduction in all cause mortality or cardiovascular hospitalization in elderly patients.(17,21)

Ivabradine is an inhibitor of the sino-atrial node by inhibiting channel if, which reduces heart rate when elevated. It has shown benefit in HFREF in sinus rhythm. Selective heart rate reduction improves diastolic filling by prolonging the diastole without significant lusitropic or inotropic effects.(20)

DIG-PEF was a randomized, double-blind, placebo-controlled trial that evaluated the effects of digoxin on all-cause mortality and on hospitalizations in patients with LVEF >45% and with normal sinus rhythm. Average follow-up was 37 months. The trial revealed that 23.4% of HFNEF patients died during follow-up because of cardiovascular causes (70%) and non-cardiovascular causes (30%). The study suggested that digoxin reduced hospitalization over the first 24 months of treatment but that it had no effect on mortality.(23)

Calcium channel blockers have been shown to accelerate ventricular relaxation in patients with hypertrophic cardiomyopathy and have been reported to directly improve diastolic LV function by decreasing cardiomyocyte cytoplasmic calcium concentration.(23)

Restriction of sodium intake and the administration of diuretics may be beneficial through reduction of LV ventricular filling pressures. They are also useful in treating hypertension, which is a common trigger for worsening HFNEF. In the Hong Kong DiastolicHeart Failure, diuretics alone appeared to be effective in reducing symptoms and improving quality of life in HFNEF patients.(23)

In the Japanese diastolic HF trial (J-DHF), the efficacy of β-blockers is being studied, and in the Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure (RELAX) trial, sildenafil (phosphodiesterase-5 inhibition) is being studied to improve clinical status and exercise capacity in HFNEF.(23)

It was found that statins may improve survival of patients with DHF (24).The use of statins should be further explored because of their abilities to prevent myocardial fibrosis and hypertrophy and to increase arterial distensibility through improved endothelial function, which may indirectly lead to improved diastolic function.

The Euro Heart Survey on heart failure was carried out between 2000 and 2001 and analyzed the case notes of 10,701 consecutive discharge or death patients diagnosed with heart failure Analysis showed that treatment with ACE-inhibitors, blockers, statins, digitalis or spironolactone did not cause a significant difference in all-cause mortality between patients with LV systolic dysfunction and those with preserved LV systolic function. The former three drug classes influenced mortality positively and glycosides influenced mortality adversely.(25)

5-Methyl-2-(1-piperazinyl) benzenesulfonic acid (MCC-135) is a compound that acts on the sarcoplasmic

reticulum by enhancing calcium uptake and reducing its leakage from the reticulum. It exerts a lusitropic effect as confirmed in animal studies. The compound is now being studied in humans. Other approaches are being tested in animal models. N-Methylethanolamine was studied in a rat model of DHF; this compound prevented myocardial stiffening through inhibition of phospholipase D activity, leading to decreased collagen synthesis. Adenoviral gene transfer of sarcoplasmic reticulum Ca2+-ATPase in senescent rats resulted in improved hemodynamic parameters of diastolic function: time constant of isovolumic relaxation and maximal rate of pressure fall.(26,27,28,29)

- **Future directions**

The PDE5 inhibitor sildenafil, which also targets ventricular–arterial stiffening and the pulmonary vasculature, currently is being tested as a treatment for HFpEF in the RELAX trial (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure). Novel agents targeting the quality or quantity of extracellular proteins such collagen, matrix metalloproteinases, and advanced glycation end products show promise, and human trials soon will be under way. Recent studies have demonstrated that a large part of the increase in diastolic stiffness of the myocyte is related to changes in the isoform and/or phosphorylation status of the sarcomeric macromolecule titin, thus novel small molecule inhibitors or activators might be engineered to affect myocyte stiffness directly.(30) The antianginal agent ranolazine, a late sodium channel inhibitor, recently was shown to reduce diastolic calcium concentration and frequency-dependent increases in diastolic tension in isolated rabbit myocytes and myocardium from humans with heart failure.(30) However, the role of diastolic calcium overload in human HFpEF remains controversial, and prospective clinical studies clearly are required before membrane-active agents such as ranolazine can be recommended for treating patients with HFpEF. The role of heart rate remains unresolved, with several studies showing that chronotropic incompetence is strongly associated with more severe exercise disability (30), whereas conventional wisdom states that heart rate should be slowed. The upcoming RESET (Restoration of Chronotropic Competence in Heart Failure Patients With Normal Ejection Fraction) trial will test the effects of rate adaptive atrial pacing in patients with HFpEF and chronotropic incompetence, shedding new light on this question.Mechanical systolic and diastolic dyssynchrony is common in HFpEF, even with a narrow QRS complex , but it remains unknown whether resynchronization therapy will ever be applicable to these patients or if this form of dyssynchrony can effectively be resynchronized at all.

Cardiac reserve function with exercise is clearly abnormal in HFpEF, and agents that restore normal cellular milieu or improve energy supply balance by affecting adenosine triphosphate flux (30) may ultimately provide more focused therapies in the future.

- **Treatment of the Underlying Disease**

When the cause of HFNEF is ischemic, standard pharmacologic treatment would be the use of nitrates, calcium channel blockers, and β-blockers. However, both a percutaneous coronary interventional technique and coronary artery bypass surgery should be considered in selected in some HF patients with coronary artery disease. Their use will result in better outcome at lower cost (quality of life improvement).(23)

If the cause of HFNEF is valvular heart disease (usually aortic stenosis), aortic valve replacement is mandatory. Surgical replacement or repair of valves relieves symptoms and improves quality of life in HFNEF (23). Relief may be gradual, in parallel with remodelling of the heart and regression of LVH following the correction of the abnormal loading conditions imposed by the LV pressure overload.

Conclusions:

HFPEF is a common syndrome, and given the epidemiology this disease will continue to increase in prevalence. Although initially there was hesitance in acknowledging the disease entity, it is now recognized that about half of all patients with heart failure have HFPEF, and the syndrome is associated with a morbidity and mortality rate that matches that of HFREF. Guidelines have been established to assist clinicians and researchers in better defining and diagnosing HFPEF. There are currently few known effective treatments available for this multifactorial and complex disorder. An effective treatment for DHF has not been established.

Novel approaches to understanding the underlying mechanisms for this disease as well as alternative treatment strategies such as treating the co-morbid illness with a multidisciplinary approach may be the key to attaining.

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