HEART FAILURE WITH PRESERVED EJECTION FRACTION: DILEMMAS AND CURRENT MEDICAL TREATMENTS

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DILEMMAS

Chronic heart failure is a growing health problem and typically refers to patients with a reduced ejection fraction. In 2001, a report on 38 patients showed that patients can develop signs of acute heart failure in the presence of a normal ejection fraction and “small hearts.” Since then, HFPEF came into focus and it is now appreciated as a serious condition with similar outcomes. About half of the patients with HFPEF are suffering from similar symptoms as those with HFREF. While the pathophysiological distinction between contractile defects in HFREF and defective filling in HFPEF provides a clear pathophysiological description, the symptoms overlap, which might be partly due to the fact that, in clinical practice, systolic and diastolic dysfunction in both conditions are usually present and rarely occur alone. An intermediate form of heart failure, HFMEF, has been recently defined by the European Society of Cardiology guidelines. Since HFPEF can develop into HFMEF and HFREF can improve to HFMEF, it is clear that this whole group of patients with heart failure is quite heterogeneous concerning ventricular mechanics and pathophysiology, which may potentially explain the difference in outcomes and treatment effects. The diversity in the clinical appearance is further complicated by a high comorbidity burden as well as the high variability in the extent and interindividual distribution in patients with HFPEF. It might have a large impact on outcomes in these patient populations by contributing to a high mortality rate, which is not much different from patients with HFREF. Finally, the cellular mechanisms of HFPEF are incompletely understood and specific cellular targets of disease-modifying therapies need to be clearly defined.

Until now, the heart failure guidelines have clearly stated that no treatments are available to improve morbidity and mortality. The majority of trials have been neutral or inconclusive. Although the pathophysiological rationale was often convincingly raised in experimental studies, showing a reduction in hypertrophy, fibrosis, and heart rate, many of these concepts have failed to show efficacy in clinical trials.
MEDICAL TREATMENTS

ACE inhibitors and AT1 antagonists
The ACE inhibitor perindopril had no effect on outcomes in patients with HFPEF. As AT1 receptors have been shown to mediate maladaptive responses, such as hypertrophy, fibrosis, and finally heart failure, ARBs were evaluated in outcome trials, which showed that they improved diastolic function, reduced myocardial hypertrophy, and improved diastolic dysfunction. The I-PRESERVE trial showed that, in patients with HFPEF, irbesartan neither improved mortality nor hospitalization rates with clearly superimposable Kaplan-Meier curves over 50 months. The CHARM-PRESERVED study showed that candesartan, while it had some effect on hospitalization rates, it had no effect on cardiovascular death. In the VALIEDD study, valsartan improved diastolic dysfunction somewhat, which was closely related to blood pressure control. Therefore, due to the lack of outcome data in HFPEF, ACE inhibitors or ARBs are not recommended beyond blood pressure control.

Mineralocorticoid receptor antagonists
Convincing data show that aldosterone mediates myocardial fibrosis, providing the rationale that fibrosis leading to myocardial stiffness and filling abnormalities might be a target for MRAs. In the ALDO-DHF trial, spironolactone improved diastolic dysfunction (E/e’ reduction), decreased left ventricular hypertrophy, and concomitantly reduced NT-proBNP levels, which did not translate into an improvement in exercise tolerance. However, spironolactone had neutral effects on cardiovascular outcomes in the TOPCAT study, which, according to a secondary analysis, might be accounted for by regional differences because, in the American population, there was a reduction in cardiovascular death and cardiovascular hospitalization, but not in Russia and Georgia, where patients were at a much lower risk and most likely were not in heart failure and did not take the drugs properly. The neutral results of TOPCAT might also have been due to a dilution effect of patients not suitable for such treatment. Future studies will try to clarify this uncertainty. The prospective outcome trial SPIRIT-HF in Germany will put particular emphasis on patient characterization and selection. Novel MRAs, such as nonsteroidal aldosterone antagonists, will also be tested.

β-Blockers and ivabradine
High heart rate is associated with an increased outcome risk for patients with HFPEF, which could only be verified in patients in sinus rhythm, but not in atrial fibrillation. Therefore, β-blockers might maintain sinus rhythm and provide a better heart rate control during exercise in patients with high heart rates. The first evidence was generated in a subgroup analysis of the SENIORS trial. The β-blocker nebivolol had a slight effect on cardiovascular outcomes, but only in the subgroup...
with an ejection fraction >40%. The ELANDD study showed that nebivolol reduced heart rate and improved oxygen consumption; however, the NYHA status did not change. Registry data provided some evidence for an improvement in mortality,\textsuperscript{9} while the OPTIMIZE-HF study showed no effect. Therefore, widespread use of β-blockers in HFPEF is not recommended.\textsuperscript{3} However, class differences, such as that observed with carvedilol, might be present, with carvedilol improving ejection fraction, outcomes, and exercise tolerance in a small underpowered trial.

In patients with HFPEF, reducing heart rate increases the length of diastole and might improve diastolic filling. Animal models show that β-receptor–independent heart rate reduction with the \( I_f \) inhibitor ivabradine improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of HFPEF. However, the EDIFY study showed no difference in \( E/e' \), exercise tolerance, and NT-proBNP levels despite a 30% reduction in heart rate. Thus, reducing heart rate per se does not improve outcomes and provides evidence that the pathophysiological concept of prolonging diastole is not applicable in patients with HFPEF.

**Calcium channel blockers**

Calcium channel blockers do not improve outcomes regardless of the class. In addition, only small trials have been performed, indicating that they have no role beyond blood pressure control.\textsuperscript{3}

**Ranolazine (late sodium current inhibitors)**

Ischemia and hypoperfusion are reported to occur in patients with HFPEF\textsuperscript{10} and are involved in the pathophysiology of heart failure by worsening the diastolic function and involving the late sodium current. Ranolazine inhibition of this current has been tested in the RALI-DHF study; however, the drug was largely ineffective with neither a decline in NT-proBNP levels nor an improvement in ventricular mechanics.

**Cardiac glycosides**

A subgroup of the DIG study on 980 patients with an ejection fraction >45% showed a trend toward a reduction in cardiovascular hospitalizations without any other beneficial effects. Therefore, there might be a role for cardiac glycosides, but only for controlling tachyarrhythmias.\textsuperscript{3}

**Statins**

The GISSI-HF study and the CORONA study did not show a positive effect of statins in patients with heart failure in general. In agreement with meta-analyses, some small studies provided evidence for lower mortality with statins.\textsuperscript{11} Since statins have not been studied in this particular condition in randomized controlled trials, there is no general recommendation.
NOVEL THERAPIES

Phosphodiesterase-5 inhibitors
The PDE5 inhibitor sildenafil prevents cardiac myocyte remodeling. However, a prospective trial in 216 stable patients with HFPEF failed to detect any improvement in exercise tolerance or clinical status after 24 weeks of treatment. Organic nitrates had no effect on quality of life, but a novel endothelial nitric oxide synthase enhancer (AVE3085) will be studied. However, until now, only experimental data are available.

Soluble guanylyl cyclase stimulators and activators
Phase 2 clinical studies have analyzed vericiguat and riociguat in patients with heart failure. Recently, the SOCRATES-PRESERVED study showed that vericiguat led to a nonsignificant change in NT-proBNP and an improvement in quality of life. Outcome studies are underway.

Sodium glucose cotransporter 2 inhibitors
In the recent EMPEROR outcome study, the SGLT2 inhibitor empagliflozin reduced cardiovascular mortality and, surprisingly, cardiovascular hospitalization (-35%), which was associated with a reduction in all-cause death (-32%). Randomized controlled studies are planned for patients with HFPEF (EMPEROR-HFPEF and EMPEROR-HFREF). Interestingly, these trials will also include patents without diabetes. Myocardial hypertrophy and HFPEF are supposed to be energy depleted due to mitochondrial electron transporter change defects. The mechanisms of SGLT2 inhibition are unclear and under discussion.

Mitochondrial stabilizers
Myocardial energy balance can be restored experimentally with so-called “Szeto-Schiller peptides (SS peptides),” such as elamipretide, which binds to the phospholipid cardiolipin in the mitochondria and stabilizes electron transport and ATP generation. There are favorable experimental data available, but the EMBRACE-STEMI study showed that SS peptides had no effect on infarct size. New results are awaited.

Novel interventions
Atrial septal stent generation, which mimics the Lutembacher syndrome, with atrial shunt devices are promising. However, long-term studies are needed, but are underway. Other techniques, such as renal denervation, cardiac contractility modulation, carotid body ablation, and baroreflex activation, are awaiting controlled studies. One option in heart failure therapy might be exercise and diet, thereby reducing the risk of HFPEF by controlling blood pressure and weight. Performing regular exercise is at the forefront of symptomatic therapies.
WHAT IS LEFT?

Diuretics
In patients with HFPEF, a total volume expansion occurs that is comparable to patients with HFREF; therefore, diuretic treatment as in decompensated HFREF is a cornerstone of symptomatic improvement in patients with HFPEF.\(^3\) It was shown that, after optimal treatment with diuretics, the addition of ACE inhibitors or ARBs had no additional effect on quality of life, exercise capacity, or myocardial function. The latter highlights the importance of optimal fluid management in patients with HFPEF. Overtreatment may be a problem because stiff hearts may depend on an adequate filling pressure, which has not been rigorously examined.

SUMMARY
The management of HFPEF is a challenge because no outcome data are available, which should not hamper efforts to develop disease-modifying strategies. Interesting ongoing studies, like those with SGLT2 inhibitors, might improve the medical treatment of heart failure. Device therapy with an atrial left ventricular shunt is promising, but safety needs to be confirmed. The ongoing PARAGON study will improve our knowledge in HFPEF after LCZ696 was tested in the phase 2 PARAMOUNT trial. The results from PARAGON are optimistically awaited. Currently, only symptomatic treatments have been shown to improve quality of life, leaving the field open for interventional techniques that reduce neuroendocrine activation and facilitate ventricular filling by improving diastolic function. Further research is eagerly awaited in order to improve the treatment of the challenging condition of HFPEF.
REFERENCES


