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Heart Failure with preserved Ejection Fraction: Defining phenotypes

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Conflict of interest:

There are no commercial products involved in this study.

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Heart failure with preserved ejection (HFpEF) has been increasingly recognized as an epidemic and various phenotypes have now been suggested (1). The clinical presentation as well as medical history may vary in this condition. Some patients experience multifold hospitalizations, and others complain of breathlessness and have a similar decrease in quality of life, but have never been hospitalized. Some patients have severe, recurrent congestion, and others are essentially symptomatic only when exercising.

The modern concept of HFpEF was proposed by Luchi et al., who in 1982 described a group of patients with typical heart failure symptoms associated with preserved ($\geq 50\%$) left ventricular ejection fraction (LVEF) (2). The heterogeneity of this syndrome was one of the reasons that several randomized studies using simple criteria did not provide evidence for effective therapies, and over the years, being wiser with the experience from these trials, we are seeking treatment strategies that could be phenotype specific for a segment of the HFpEF population (3-5). The array of tested remedies is quite vast and still increasing, including both pharmacological agents and implantable devices (6).

Recently, HFpEF has been re-defined by the European Society of Cardiology (ESC) as preserved left ventricular EF (LVEF $\geq 50\%$), with evidence of diastolic dysfunction and structural heart disease, in the context of elevated biomarkers, and classic signs and symptoms of heart failure (1). The importance of echocardiography and dynamic testing is reflected in the score that is the essence of the proposed diagnostic algorithm (7). By using a comprehensive, alternative-based evaluation process, this new approach improves the accuracy of HFpEF identification, and probably is more effective in identifying the “never-hospitalized” patients who are complaining mainly of exertional dyspnea. On the other hand, it does not permit a priori stratification of

patients according to the occurrence and severity of symptoms. Other scores and pathophysiologically-based diagnostic approaches have been proposed, but their relevance in the context of patient selection for interventions providing symptomatic and prognostic improvement has not been validated (8-10).

The manuscript by Reddy et al in the current issue of the Journal deserves special attention and careful analysis (11). It is based on 7 NIH sponsored multicenter trials in HFpEF and focuses on the distinction between patients with and without HF hospitalization. The hospitalization phenotype is characterized by a larger burden of non-cardiac pathologies including more advanced renal dysfunction, COPD and anemia, more impaired functional capacity and worse outcomes. Interestingly, the quality of life and resting echocardiographic profile are similar in both subsets stratified on the basis of hospitalization history. Nevertheless, these observations might suggest that the 2 categories may require different management approaches, with multi-organ protection and prevention of recurrent congestion in the “hospitalized” group vs. a focus on improving exercise capacity in the “never-hospitalized” subset.

The authors emphasize that it is not clear whether these 2 groups of patients represent the same disease process at different stages or different clinical phenotypes (figure 1). A potential transition from the less-diseased to the more-diseased HFpEF category was previously postulated but is not proven (12). As a consequence, if the contribution from the non-cardiac organs to the disease process is not a distinctive feature of the “hospitalized” phenotype, approaches that prevent the progression of extra-cardiac pathologies should be considered in patients with HFpEF who have never experienced a HF hospitalization. As a consequence in

might be important to search for the common denominator contributing to the progression of multi-organ abnormalities e.g. systemic inflammation (13).

The current paper is a retrospective, multi-trial analysis, in which the extent of echocardiography use was limited by the protocols of the original studies. It is likely that the inclusion of additional echocardiographic parameters, especially LV and LA strain, and RV/pulmonary indices, might have improved the characterization of clinically-derived phenotypes and provided more information relevant for decision-making. Furthermore, an important source of prognostic data in patients without HF hospitalization would have been exercise echocardiography, with quantification of LV diastolic and systolic responses to exertion. Accordingly, extended imaging might add to the “macroscopic” phenotyping proposed by Reddy et al (11, 14).

Despite this limitation, the results set the stage for further studies. What were the results of PARAGON -HF in non-hospitalized patients(15)? Given the vasodilating properties of sacubitril/valsartan, this treatment could be more beneficial in patients who need more afterload reduction than a decrease in fluid retention. The relative and absolute benefits of sacubitril/valsartan compared with valsartan alone in HFpEF appear to be amplified when initiated in the high-risk window after hospitalization. On the other hand, patients hospitalized or recently hospitalized might require a more aggressive diuresis by agents that are safe for the kidney and liver like the gliflozins (16). Accordingly, the work by Reddy et al. may facilitate the interpretation of trial findings and provide guidance on specific treatment approaches (11).

Another issue that needs to be addressed is the clinical impact of atrial fibrillation, as well as the approaches to the management of this arrhythmia in both HF hospitalization-based phenotypes. The presence of atrial fibrillation may be an important component of the phenotypic profiling in HFpEF and should be taken into account when planning therapeutic strategies (17).

To summarize, the current contribution underscores once again the need for phenotype-specific therapy in patients categorized as having HFpEF. The presence of HF hospitalization in the patient history is a powerful determinant of the clinical presentation and outcome. The putative pathophysiological differences between patients with HFpEF with and without HF hospitalizations need to be more profoundly explored in future studies. The potential therapeutic implications of this approach to HFpEF heterogeneity based on the history of HF hospitalization might be worth considering to improve patient management. We believe that the wider use of echocardiography in the phenotyping process may aid in establishing efficient treatments in this highly prevalent condition.

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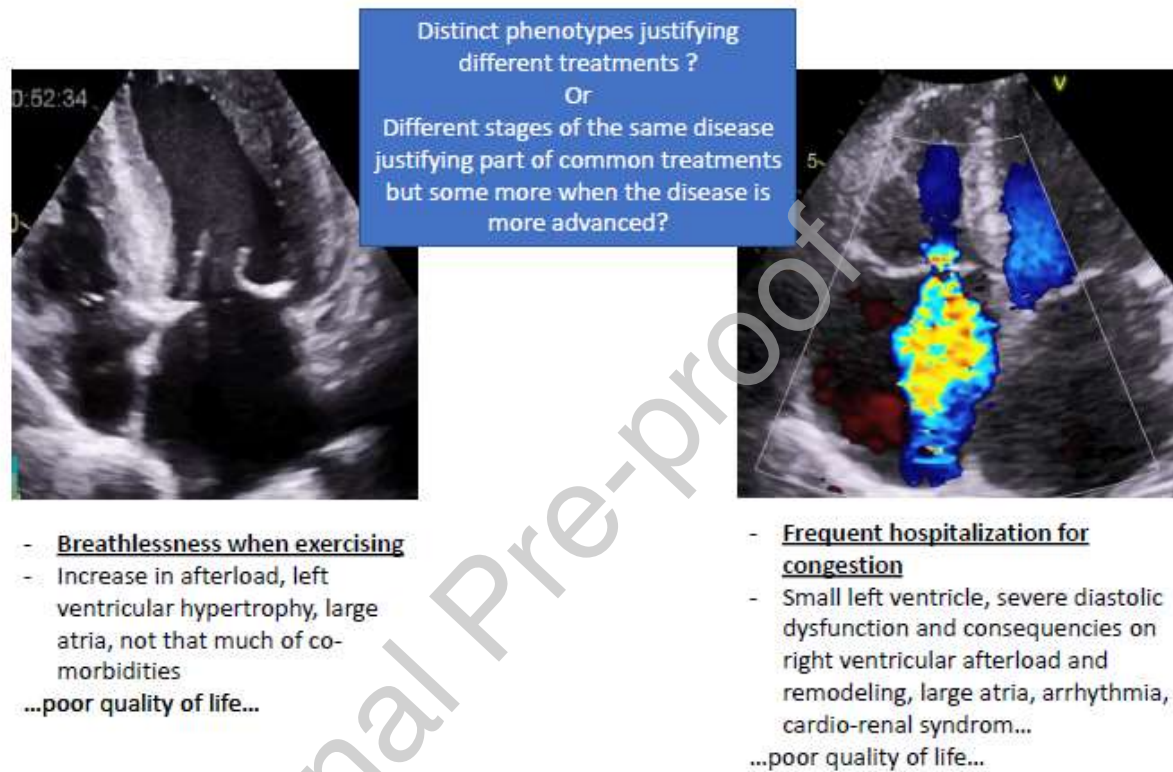


Figure 1: two phenotypes with distinct pathophysiology or two stage of the same disease?