The pursuit of understanding Heart Failure with preserved Ejection Fraction (HFpEF)

11

VALORIZATION

SOCIO-ECONOMIC RELEVANCE

Affecting 26 million people worldwide, heart failure (HF) is the leading cause of hospitalization among older adults and one of the major causes of death and disability [1]. In the following years, due to aging, the increase of comorbidities and the improvement of survival due to therapeutic advances, it is expected that the prevalence of HF will continue to increase [2]. Despite therapeutic advances, HF morbidity and mortality remain unacceptably high, being the first cause of hospitalization above 65 years from which only a quarter to one third survive 5 years after admission [3]. Consequently, HF represents an important health care burden and is responsible for 1-2% of the health care expenses in Europe or United States [4].

Around one half of HF patients suffer from HF with preserved ejection fraction (HFpEF). Ageing and an increase of comorbid conditions have made that HFpEF has become a serious health care problem with 1% incidence increase per year [5]. Patients with HFpEF are older, more often women and present a higher rate of comorbid conditions such as diabetes, hypertension or atrial fibrillation [6, 7]. Many efforts have been focused on elucidating the nature of this disease and trying to find effective treatments. The heterogeneity of HFpEF with different clinical phenotypes and the poor understanding of the underlying pathophysiology is the main reason why no effective treatments have been found yet. Until date, numerous trials have shown that the classical one-size-fits-all strategy is not effective for treating HFpEF. Elucidating and understanding the matrix relating clinical phenotypes and underlying pathophysiological mechanisms is essential to find targeted, phenotype-specific HFpEF treatments. Finding effective treatments which improve prognosis in HFpEF is desperately needed for improving quality of life and prognosis of HFpEF patients, and also to decrease health care expenses which otherwise will increase even further.

In this thesis we aim to provide an overview of the current knowledge about HFpEF and the unanswered gaps, as well as we focus on different steps that should be taken to pursue the objective of finding effective treatments for HFpEF. First, diagnosing HFpEF is key. If we are not able to determine which patients suffer from the disease, an amalgam of individuals will be included in clinical trials, influencing the effects of any treatment strategy. Although different diagnostic guidelines and algorithms have been proposed, diagnosing the disease remains difficult. Therefore, specialized outpatient HFpEF clinics, with clear diagnostic work-up pathways are necessary. Moreover, a national collaborative network system between primary, secondary and tertiary or 'reference' centres is important to evaluate and share results and knowledge with the aim of improving the whole process.

Secondly, comorbidities play a central role in HFpEF, but, like different population-based studies show, HFpEF is more than a compilation of comorbidities [8, 9]. Increasing knowledge and understanding the role comorbidities play in HFpEF, which mostly are not single players, is key for novel trial designs. Phenotype based targeted therapy, currently the only hope for treating HFpEF, first requires proper clinical phenotyping. Understanding pathophysiological aspects of the disease like the role of microvascular dysfunction in HFpEF, but also in incipient stages of the disease like prediastolic dysfunction (PDD), can open the door to novel diagnostic and treatment strategies.

Finally, enhancing translational research and matching complex animal models with human HFpEF phenotypes provides a unique opportunity to develop and test novel targeted treatments. Furthermore, we propose which innovative trial designs could be most useful to achieve the goal of finding effective, personalized targeted therapy in HFpEF.

TARGET GROUPS

The results of this thesis are important for HF patients, but also to cardiologists, pulmonologists, internists, general practitioners and the scientific community. First of all, this thesis creates awareness. It also proposes systematic diagnostic strategies and clinical phenotyping as the first step for designing novel trials in which targeted therapy can be tested. All these steps concern HF patients, more specifically those suffering from HFpEF, but also patients suspected of suffering from HFpEF. Furthermore, a better understanding of the pathophysiology, which has not been only evaluated in HFpEF, but also in patients at risk of developing the disease, extends the targeted group to all individuals at risk of developing HFpEF. Besides patients, medical professionals including cardiologists, other specialists concerned with HFpEF (such as pulmonologists or internists), and general practitioners benefit from the concepts developed in this thesis. Finally, the development of complex animal models and how these models can be linked to clinical and pathophysiological phenotypes will be crucial. Furthermore, novel trial designs and their role in future research projects as well as the major steps concerning elucidation of pathophysiological processes involved in HFpEF are of special interest for the scientific community.

ACTIVITIES, PRODUCTS AND INNOVATION

During this thesis, one of the main objectives has been to create awareness and to explain what that great unknown, called HFpEF, is to patients, cardiologists, other medical specialists and general practitioners. We believe specialized HFpEF outpatient clinics are the only way to phenotype patients and develop targeted therapy.

In addition, in this thesis we show that iron deficiency (ID) influences prognosis in HFpEF. Impaired exercise capacity, however, is not only related to ID, but is multifactorial. These results stress out the importance of the systematic and deep phenotyping in HFpEF. In this example, only patients with specific comorbid conditions related to ID-HFpEF, like pulmonary hypertension as independent predictor of both ID and exercise capacity, could respond to intravenous iron therapy.

Finally, the finding that HFpEF patients present with altered coronary microvascular function and peripheral muscle metabolism in comparison to hypertensive controls, supports the theory that HFpEF is a systemic disease, affecting not only the heart but also skeletal muscle metabolism. These novel results open the door to future trials in which specific exercise training or pharmacological strategies could be tested. For example, Just like it has been shown to be effective in improving angina, stress exercise testing, myocardial perfusion, coronary endothelial function, and microvascular function in patients suffering from myocardial non-obstructive coronary artery disease (MINOCA), maximum intensity statins and maximum tolerated angiotensin converting enzyme inhibitors or angiotensin receptor blockers could be also effective in selected HFpEF patients [10].

PLANNING AND IMPLEMENTATION

Although important achievements have been made in understanding and diagnosing HFpEF, there is still a long way to go. The goal for the next decade is to find effective treatments that improve quality of life and prognosis of HFpEF patients. Deep phenotyped HFpEF cohorts will be key to analyse the different pathophysiological processes linked to each clinical phenotype. But currently, the Maastricht HFpEF cohort is one of the few prospective cohorts worldwide with suspected HFpEF patients with a true consecutive, prospective inclusion and extensive diagnostic evaluation. The implementation of specialized HFpEF outpatient clinic programs can change this picture, and can be used as the first step to build up larger well phenotyped HFpEF cohorts. Furthermore, Multiple Criteria Decision Analysis (MCDA) based on cluster analysis, performed in these well phenotyped HFpEF cohorts, will play an important role in identifying the different clinical phenogroups and correlating them to biomarkers that could be used for diagnostic, therapeutic or prognostic purposes. In this regard, the Maastricht HFpEF cohort has biobanking, where biological samples of patients suffering from HFpEF but also controls have been stored. This samples will be used in future projects focused on studying biomarker and DNA profiles and DNA. Both, biomarkers and DNA can be helpful for a better understanding of the underlying pathophysiology and consequently improve diagnosis. Furthermore, discover and validate biomarkers in early stages of the disease, such as in PDD, can identify and stratify those patients allowing to implement treatment strategies in an early, reversible stage of the disease.

As we show in this thesis, coronary microcirculation is altered in HFpEF patients. Our study in chapter 8 was not sufficiently powered, however, to address peripheral microvascular function. The ongoing "HFpEF and peripheral microcirculation study" (METC 19-005) will try to evaluate if there is a difference in peripheral microvascular and macrovascular function between HFpEF and controls without HF.

There are also ongoing projects focused on iron deficiency and peripheral muscle metabolism. The "Iron Muscle study" (METC 181034) is currently recruiting HFpEF patients with and without iron deficiency, to study if iron deficiency effects skeletal muscle metabolism, as measured by Magnetic resonance spectroscopy.

Science communication, as an exercise to communicate and share scientific knowledge and research results, is of enormous importance in a field such as HFpEF. The development of the Maastricht HFpEF cohort and the results of the different studies have been presented at national and international congresses. Education sessions for general practitioners have been organized and regional cardiologists have been informed about the development and scientific achievements of the Maastricht HFpEF cohort. Furthermore, we have actively informed the local community through articles and interviews in local news media, and we have actively participated in patient meetings.

The market is waiting for effective drugs for treating HFpEF to be found. However, negative results obtained by all clinical trials until date have created a pessimistic scenario that needs to be turned around. To create a more encouraging setting and achieve our goals, the strategies that have been used until date have to change. In order to fully understand the disease, phenotyping and classifying patients will be key.

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