Why Don’t We Have Proven Treatments for HFpEF?

Jason Roh, Nicholas Houstis, Anthony Rosenzweig

The lack of effective treatments for heart failure with preserved ejection fraction represents a large and growing unmet need in cardiology today. A critical obstacle to therapeutic innovation in heart failure with preserved ejection fraction has been the absence of animal models that accurately recapitulate the complexities of the human disease. Here, we propose that more comprehensive multiorgan system and functional phenotyping of preclinical models is essential if we are to maximize our chances of discovering and validating novel targets for effective therapeutic development in heart failure with preserved ejection fraction.

At this time in human history, we are witnessing an unprecedented aging of populations around the world. By 2050, the number of individuals >65 years will nearly triple to ≈1.5 billion, accounting for ≈16% of the world’s population. Although cardiology, and medicine more generally, can appropriately take enormous pride in the progress made in extending human lifespan, we must also recognize that as our populations age, so will the clinical landscape.

Perhaps the quintessential example of how the evolution of human longevity is changing the face of medicine is the emerging epidemic of heart failure with preserved ejection fraction (HFpEF). Often described as a disease of the elderly, trends in HFpEF have closely paralleled the change in global ageing demographics. In the United States, the prevalence of HFpEF, relative to heart failure with reduced ejection fraction (HFrEF), is increasing at an alarming rate of 1%/y with the overwhelming majority of patients being >65 years. Importantly, the prognosis for HFpEF remains poor with mortality rates comparable with HFrEF.

Unfortunately, although tremendous strides have been made in improving mortality in HFrEF, no pharmacological therapy, including our armament of neurohumoral antagonists, has demonstrated similar benefits in HFpEF. In fact, no large-scale clinical trial of medical therapy has met its primary end point in HFpEF.

Why have we failed to develop effective treatments for HFpEF? Although various hypotheses have been proposed, central to all of them is the issue of heterogeneity. At a fundamental level, this refers to the multifactorial nature of HFpEF pathophysiology. Initially thought to be due primarily to diastolic dysfunction, beautifully conducted human studies during the past 20 years have called into question this simplistic view, demonstrating that HFpEF encompasses a complex interplay of multiple impairments throughout the body. These involve not only diastolic function but also cardiac reserves, systemic and pulmonary vascular function, renal function, oxygen carrying capacity, and peripheral oxygen extraction. Complicating matters further, the degree to which each of these systems is altered, and hence, the relative impact of each one on symptoms, can vary markedly from patient to patient, raising the other major issue of heterogeneity in HFpEF—is this one condition or many?

Perhaps it is not surprising that a clinical condition defined largely by the absence of overt systolic dysfunction, together with common symptoms, such as dyspnea, is heterogeneous at multiple levels. Although this has made HFpEF particularly difficult to study, recognizing this core concept has enabled human studies to make steady progress dissecting its pathophysiology. Unfortunately, this appreciation of heterogeneity has not carried over to preclinical investigation. For the most part, the diverse spectrum of findings identified in HFpEF patients have not been explored in animal models, which have primarily focused on diastolic function. We think this represents a major shortcoming in the field that impedes our ability not only to identify key molecular mechanisms but also to develop much-needed therapies for HFpEF.

Although the value of animal models has been questioned in recent years, in many settings, they have provided an essential bridge to understanding disease pathophysiology and developing effective therapeutics. This is perhaps particularly relevant in cardiovascular disease, given the intricate connection between disease and cardiovascular physiology, as well as limited access to clinical tissue samples. Indeed, one of the cornerstones of HFrEF therapy originated from a rat myocardial infarction model developed by Pfeffer et al in the 1970s. This seminal work not only refined our understanding of the renin–angiotensin–aldosterone system in post myocardial infarction remodeling, but also demonstrated the efficacy of renin–angiotensin–aldosterone system inhibition and laid the foundation for clinical trials and deployment of these interventions in ischemic heart disease and HFrEF.

To achieve similar success in HFpEF, we think a vital tool will be animal models that capture a hallmark feature of the disease, namely multiple system pathologies. Although systemic impairments are evident in both HFpEF and HFrEF, the cause of these deficits seems different, which has significant implications for modeling these diseases in animals. In HFrEF, systemic pathologies are largely driven by a primary defect in systolic function, which can be induced in animals with clinically relevant interventions, such as coronary artery ligation. In contrast, it remains unclear whether a single
cardiac or systemic defect can reproduce the many systemic phenotypes seen in HFpEF. Thus identifying models that capture the broad spectrum of phenotypes seen in HFpEF patients provides our best hope of investigating and validating causative mechanisms.

Although seemingly intuitive, this approach to modeling has not been routinely pursued in preclinical HFpEF studies. For a detailed review of animal models of HFpEF, we refer the interested reader to the following literature. For the most part, these models have focused on using comorbidities commonly associated with HFpEF to induce a single cardiac-specific phenotype frequently seen in patients. For example, induction of hypertension through surgical, dietary, or genetic interventions, followed by assessing its impact on cardiac hypertrophy or diastolic dysfunction is a common approach to studying HFpEF in animals. However, is this HFpEF? Although diastolic dysfunction is certainly part of the compendium of HFpEF phenotypes, it is only 1 piece of the puzzle. Moreover, many HFpEF patients actually have normal cardiac dimensions, and not all individuals with diastolic dysfunction have HFpEF. We think that animal models that recapitulate 2 or more HFpEF phenotypes (eg, diastolic dysfunction and impaired exercise capacity) would be more faithful to the disease and more likely to yield clinically useful insights. Such models could be used to identify common biological mechanisms driving multiple pathologies. Moreover, when testing novel therapies, such animal models would also permit a multidimensional phenotypic readout of therapeutic efficacy, which could help identify patient subgroups most likely to benefit from a specific intervention.

To identify animal models with multiple system impairments, it will be critical to comprehensively phenotype existing and new models for the pathologies that have been implicated in patients. These phenotypes include alterations in cardiac morphology (hypertrophy, fibrosis, capillary density), systolic and diastolic function, cardiac reserves, macro- and microvascular function, pulmonary physiology, immune regulation, oxygen utilization, renal function, and skeletal muscle function. Importantly, some impairments in cardiopulmonary, vascular, or peripheral function in HFpEF are not evident at baseline but require physiological stress, such as exercise, to unmask. This explains why the hallmark symptoms of this condition are typically elicited only with exertion or hemodynamic perturbations. Many clinical studies of HFpEF have recognized the importance of this concept and incorporated exercise testing to quantify impairments in physiological reserves that could explain symptoms. However, in contrast, most preclinical studies have relied solely on resting cardiac functional assessments. Moreover, these assessments are typically conducted in anesthetized animals further confounding the interpretation of hemodynamic and functional results. When combined with cardiac imaging or hemodynamic monitoring, exercise testing can provide tremendous insights into an animal’s physiological reserves. Indeed, measuring exercise capacity integrates functional assessment of many of the previously mentioned HFpEF phenotypes, and is closely related to dyspnea on exertion, the cardinal HFpEF symptom. In the search for mechanisms of disease, we think that the discoveries most likely to translate to patients will be those that causally link pathophysiology to functional phenotypes. For all these reasons, we think that exercise testing should be routinely incorporated into the evaluation of animal models of HFpEF.

We propose that more comprehensive characterization of preclinical HFpEF models, through multiorgan system phenotyping and physiological stress-based functional testing, is necessary to identify better models of the human condition and bridge the large translational gap between animal and human HFpEF studies. In particular, as the utilization of high-throughput screening platforms continues to expand, we will likely find numerous promising biomarkers associated with clinical outcomes and HFpEF phenotypes. Determining which if any of these biomarkers play causal roles in HFpEF and thus represent targets for therapeutic intervention will require well-phenotyped animal models in which we can rigorously study molecular mechanisms and the consequences of intervention. In HFpEF, just as in any other complex multisystem disease, understanding the interaction between the various phenotypes becomes just as important as the phenotype itself. For example, assessing an intervention’s impact on cardiac hypertrophy is not sufficient to establish its role in HFpEF pathophysiology or its efficacy as a therapeutic target. The impact of the intervention would also need to be assessed on other phenotypes, such as diastolic function and cardiac reserves, and ultimately on pulmonary congestion and exercise intolerance, the final mediators of HFpEF symptoms. Of course, this can only be accomplished if the multiple phenotypes of HFpEF have already been characterized in our animal models.

In summary, although many questions regarding HFpEF pathophysiology remain, we are making headway through clinical investigation that is expanding our once cardio-centric perspective into one that recognizes multisystem contributors to HFpEF. However, continued progress will require parallel advances in basic and translational investigation. At this juncture, the development and comprehensive characterization of animal models is one of the biggest roadblocks to advancing our understanding of HFpEF, as well as to the identification and evaluation of novel therapeutic approaches for this condition. To address this shortcoming, we think that there should be greater emphasis on the comprehensive evaluation of multiple HFpEF phenotypes both at baseline and in response to relevant physiological stress. Until we have well-established animal models, we are unlikely to change the trajectory of the growing HFpEF epidemic in our aging populations.

**Sources of Funding**

This study was supported by the Frederick and Ines Yeatts Fund for Innovative Research, American Heart Association 16FF29630016 Award (Dr Rob); Margaret Q Landenberger Foundation Award (Dr Houstis); and grants from the National Institutes of Health (R01HL122987, R01HL110733) and an American Heart Association Strategically Focused Research Network Heart Failure Center Award (Dr Rosenzweig).

**Disclosures**

None.
References


Key Words: aging ▪ cardiology ▪ exercise ▪ heart failure ▪ models, animal
Why Don't We Have Proven Treatments for HFpEF?
Jason Roh, Nicholas Houstis and Anthony Rosenzweig

Circ Res. 2017;120:1243-1245
doi: 10.1161/CIRCRESAHA.116.310119
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/120/8/1243

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/