Inflammation in Heart Failure With Preserved Ejection Fraction

Time to Put Out the Fire*

Mardi Gomberg-Maitland, MD, MSc,a Sanjiv J. Shah, MD,b Marco Guazzi, MD, PhDc

Heart failure with preserved ejection fraction (HFpEF) is a common and costly condition associated with a high frequency of comorbid conditions. HFpEF prevalence is rising compared to heart failure with reduced ejection fraction (HFrEF), without any change in clinical outcomes over the past 20 years (1).

In contrast to HFpEF, HFrEF outcomes have improved with the advent of multiple drug therapies. Most of the therapeutic approaches proven to be effective in HFrEF have been tested and developed in controlled experimental studies in animal models (2) by dissecting the role of abnormal signaling in intracellular molecular pathways (3). The most impressive examples come from studies on angiotensin-converting enzyme inhibitors and beta-blockers. Mechanistic research enabled appropriate therapeutic targets and favored the development of genetically manipulated small animal strains (3).

Thus far, therapeutic remedies have been ineffective in HFpEF likely because a multitude of phenotypes are grouped under the same definition (4). Another central reason for the lack of therapies for HFpEF may be related to the erroneous assumption that the therapeutics approved for treating HFrEF can be successfully transposed to HFpEF without a full appreciation of differences in cardiac adaptation and extent of diastolic impairment (5) or, more simply, without taking full advantage of translational science and appropriate animal models. Indeed, animal models of HFpEF are not as well established as many capture components of specific hemodynamic aspects, such as left ventricular (LV) vascular uncoupling (6), left atrial dysfunction, and pulmonary hypertension (7), but poorly reproduce the integrative complexity of human disease and related comorbidities such as obesity, diabetes, chronic kidney disease, and atrial fibrillation.

As systemic inflammatory state is central to these common comorbidities associated with HFpEF and oxidative stress and endothelial dysfunction are prominent features that characterize the so-called metabolic risk, especially in the presence of obesity (8). It is noteworthy that occurrence of an inflammatory activation is predictive of incident HFpEF but not HFrEF (9). Once exposed to inflammatory activation, the cardiac myocyte suffers from an impaired cellular signaling at a variety of levels. Specifically, endothelial dysfunction in the coronary microcirculation may alter the paracrine cross-talk signaling between coronary circulation and cardiomyocyte through decreased bioavailability of nitric oxide (NO) and its downstream cyclic guanosine monophosphate (cGMP) protein kinase G (PKG) pathway (10). Collagen turnover and titin homeostasis critically depend on cGMP and PKG signaling, which is absolutely relevant for passive properties (stiffness) of the LV, as demonstrated in animals, isolated human cardiomyocyte preparations (11,12), and the intact human myocardium (13). Recent research suggests that coronary microvascular endothelial inflammation is

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From the aCardiology Section, Department of Medicine, University of Chicago, Chicago, Illinois; bDivision of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and the cCardiology Department, University of Milan, I.R.C.C.S. PoliClinico San Donato, San Donato Milanese, Milan, Italy. Dr. Shah has received research grant support from the National Institutes of Health (R01 HL107557 and R01 HL127028), Actelion, and Novartis; and has served as a consultant for AstraZeneca, Bayer, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
also associated with coronary microvasculature rarefaction, with a resultant reduction in capillary density that may impair coronary flow reserve, thereby causing LV systolic and diastolic dysfunction (14). According to this emerging evidence, inflammatory activation and its multisignaling cascade of events on the coronary microvasculature and myocardium is increasingly recognized as a primary contributor in the pathogenesis of HFpEF, and thus has become an intriguing target for intervention (15).

In this issue of *JACC: Heart Failure*, Franssen et al. (16) provide further demonstration of the putative role of myocardial microvascular inflammation in HFpEF by studying its effects on cardiac myocyte oxidative stress and NO pathway signaling in a parallel human and animal study. The authors designed an elegant study that included analysis of myocardial biopsies from a group of patients with increased body mass index and left ventricular hypertrophy (LVH) associated with HFpEF and 3 comparison groups: nonobese HFrEF, aortic stenosis, and control groups. The results of the human study were compared with findings obtained in 2 strains of ZSF1 rats—one leptin resistant, obese, hypertensive, and diabetic and the other nonobese, nondiabetic, and hypertensive. The ZSF1 leptin-resistant model develops LVH and signs of HF, increased LV filling pressure, myocyte stiffness, and congestion, with preservation of LV ejection fraction.

The authors found a similar inflammatory phenotype in HFpEF patients and ZSF1 obese rats, with the same expression of adhesion molecule (ICAM-I, E-selectin), oxidative stress (increased H2O2 and...
reduced nitrite/nitrate concentration), and evidence of uncoupling of endothelial NO synthase. Findings typical of the HFP EF phenotype were not present in the HFrEF and aortic stenosis biopsy samples.

The HFP EF human “metabolic phenotype” adopted in this study was highly selected (body mass index >30 kg/m², hypertension, and diabetes) reproducing the most frequent constellation of comorbid disorders in HFP EF (17). Compared to previous observations by the same group (18) the findings of the present study have been extended to a wider characterization of molecular arrays, particularly the multilevel examination of microvascular inflammation, oxidative stress, NO-cGMP-PKG signaling, and titin analysis. The more extensive characterization of the molecular cascade allows us to draw solid conclusions on the associative and, in part, mechanistic role of these pathways in the context of the human HFP EF syndrome.

Because HF is by definition a syndrome with sign and symptoms of congestion, a full characterization of congestive state in both human and animals would have been useful especially considering that the patients included in the present study were hospitalized for an acute episode of decompensated HF whereas the rats that were studied had a more chronic, progressive congestive state. On the basis of the results of the study, these differences in the human subjects versus animal models do not appear relevant in terms of inflammatory activation; however, on the basis of the association of inflammatory markers such as C-reactive protein with the severity of LV end-diastolic pressure increases in HF (19), documentation of the severity of congestion in the patients and the animals in the study could have helped with understanding whether the authors’ results were more applicable to a more advanced stage of HFP EF.

The study by Franssen et al. (16) also could have benefited from a more detailed analysis of cardiac structure and function; indices such as degree of LVH, type of remodeling, and cardiac mechanics were lacking both in the humans and animal models included in the study. How much passive stiffness is affected by inflammatory activation per se rather than pressure overload and ventricular-vascular uncoupling in the in vivo setting remains an unanswered question.

Why is this study important and how do these parallel human and basic science analyses enhance knowledge in the field? The study not only elucidates potential causative metabolic processes but also helps us as clinical investigators better design clinical trials. Limiting our early-phase HFP EF therapeutic trials to patients with only certain comorbidities, similar to these animal models, may result in a more targeted clinical trial approach with early mechanistic studies in limited numbers of patients (i.e., T1 phase trials). An iterative, nimble exchange between animal studies and T1 human studies could result in more fruitful phase 2 and 3 HFP EF clinical trials (Figure 1). If successful this type of strategy would also help validate the use of specific animal models for HFP EF. Despite a few drawbacks, the findings by Franssen et al. (16) remain meritorious because they add evidence to the emerging prominent role of inflammatory activation in HFP EF and recall the necessity to optimize the bench to bedside methodological gaps at a level equivalent to what has been successful for HFR EF (i.e., establish animal models that may accurately reproduce the cellular pathways closest to the specific human failing heart phenotype and associated comorbidities). These emerging perspectives and an extended profiling of the cGMP-PKG signaling cascade seem preparatory to appropriately match anti-inflammatory therapeutic interventions to the “inflamed” HFP EF phenotype in large-scale clinical trials.

REPRINT REQUESTS AND CORRESPONDENCE TO: Dr. Mardi Gomberg-Maitland, Section of Cardiology, University of Chicago, 5841 South Maryland Avenue, MC 5403, Chicago, Illinois 60611. E-mail: mgomberg@bsd.uchicago.edu.


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