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EDITORIAL COMMENT

"Circulating Inflammation" and the Plasma Proteome in Heart Failure With Preserved Ejection Fraction

Thomas M. Vondriska, PhD,[a] David J. Lefer, PhD[b]

A heart failure diagnosis characterizes a multietiologic syndrome with risk factors including uncontrolled hypertension, coronary artery disease, atrial fibrillation, type 2 diabetes, and aging. Recent clinical and translational research has focused on the observation that ~50% of patients exhibit heart failure with preserved left ventricular ejection fraction (HFpEF) and not heart failure with reduced ejection fraction (HFrEF). Established therapies to treat HFrEF have yet to similarly improve clinical outcomes in HFpEF and yet HFpEF is increasingly prevalent,[1] due in part to the reduction of ischemic HFrEF by revascularization therapy but also exacerbated by a global obesity and diabetes pandemic.

Unlike hypertrophic or dilated cardiomyopathies, which have principally genetic origins, the forms of common, acquired heart failure described above lack well-defined genetic causes and result from a complex genetic susceptibility that affects one or more of the disease triggers. For example, genetic variation linked to HFpEF and HFrEF in humans displays differential association with individual heart failure risk factors like atrial fibrillation, body mass index, coronary artery disease, and ventricular function.[2,3] Dense clinical data can improve subtyping of so-called phenogroups of HFpEF patients,[4] which display distinct clinical outcomes and are increasingly recognized as a critical determinant of effective management.[5] The role of genetic variation in precipitating these phenogroups is unknown, but likely affects both their incidence and their responsiveness to therapeutic management. It is noteworthy that the very concept of genetic contribution to a syndrome like HFpEF is protean; body mass index, appetite, blood pressure, and lipid metabolism are all multi-genic phenotypes, with genetic causes that—with rare exception (eg, individuals with PCSK9 mutations)—almost always have a small effect on phenotype. In other words, minor genetic effects, spread across multiple predisposing conditions, each with varied contribution depending on ethnicity, social-economic background, diet, exercise, and other environmental factors, mean that understanding the genetic contribution to HFpEF as a syndrome is very challenging.

In their paper in this issue of *JACC: Basic to Translational Science*, Giro et al[6] asked the question of whether plasma proteome changes may underlie the pathophysiology of increased susceptibility to HFpEF in individuals with a missense mutation in intracellular adhesion molecule (ICAM)-1, a cell surface glycoprotein expressed on leukocytes and involved in the inflammatory responses of these cells. This particular mutation, rs5491 p.K56Me, is common only in African Americans (minor allele frequency ~20%, according to the paper) and is associated with increased expression of ICAM-1 and increased risk for HFpEF. Intriguingly, another mutation in ICAM-1 (rs5498; p.K469E) also increases ICAM-1 protein levels regardless of ethnicity but is not associated with HFpEF. Reasonably, the authors hypothesized that increased ICAM-1 expression in rs5491 mutant-carrying individuals would lead to a proinflammatory subproteome.

The authors took a "targeted" approach, focusing on association of the 15 proteins they selected as

From the [a]Departments of Anesthesiology & Perioperative Medicine, Physiology and Medicine, David Geffen School of Medicine, Molecular Biology Institute, University of California-Los Angeles, Los Angeles, California, USA; and the [b]Department of Cardiac Surgery, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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inflammation related, followed by an "untargeted" approach, in which all 92 proteins on the immunoassay platform used in the study were examined. (In actuality, both approaches are targeted and examine a miniscule portion of the entire proteome. There are thousands of proteins in plasma that are not measured in this experiment and there are undoubtedly proteomic changes within the cells expressing ICAM-1 that in turn influence inflammation, or other processes, that precipitate HFpEF. But from a discovery standpoint and considering feasibility, this approach makes a lot of sense.) Seven of the proteins in the targeted approach showed significant association with the variant that, along with principal component analysis, was used to identify signaling by tumor necrosis factor, a well-characterized intercellular inflammatory signaling pathway, as significantly associated with the rs5491 mutant. When all the 92 proteins were analyzed between the samples, considerable variability was observed and weighted coexpression network analysis was used to extract hierarchical relationships between modules of coregulated proteins. Within the modules produced by this analysis, substantial variability existed in terms of correlation with individual clinical phenotypes. In other words, targeted proteomics revealed connections of proteins with each other based on differential expression between mutant and wild-type alleles, yet the connection between these protein networks and clinical phenotypes remains unclear. The authors further use the modules of proteins to explore associations with specific echocardiographic measurements, several of which are unique in their positive association with the rs5491 mutant. Lastly, validation analyses in a separate study population (Atherosclerosis Risk In Communities study) also provide evidence of association between presence of the rs5491 mutant and inflammatory pathways.

Although not reported across the patients in this study, the assumption based on previous work is that either the rs5491 or the rs5498 mutation alone is sufficient to increase ICAM-1 protein levels. How, then, is it possible only rs5491 is associated with HFpEF and activation of an inflammatory subproteome in the plasma? It may be that ICAM-1 activity, in addition to total expression, is also affected by the mutation in a manner that influences HFpEF symptoms (rs5491 converts a lysine to methionine at position 56, whereas the rs5498 mutation converts a lysine to glutamine at residue 496). Part of the answer may also be that the rs5491 mutation, enriched in African Americans, has its effects in concert with changes induced by other common mutations or nongenetic factors—not measured in this study—present in this population but uncommon in individuals not identified as African American.

How to use this information? One approach may be to subgroup HFpEF patients based on the presence of an inflammatory subproteome and prioritize these patients for inclusion in trials of targeted anti-inflammatory drugs. This study does not reveal a linear relationship between ICAM-1 levels, inflammation, and individual clinical phenotypes in HFpEF, in agreement with other recent studies.[7] Although it is true that individuals carrying the rs5491 allele had greater levels of a targeted subproteome of inflammatory proteins (tumor necrosis factor-associated proteins, in particular), which phenotypes these genes are associated with and in which cells the proteins are operative remain untested in this paper. Thus, whether individuals with HFpEF and the rs5491 allele would benefit from anti-inflammatory therapy is unknown, but this study suggests that any such trial must pay close attention to individual markers of HFpEF, such as E/E' (a measure of ventricular stiffness), which had a strong association with the allele.

HFpEF is huge human health and economic burden with increasing incidence due to obesity and hypertension. It is also a systemic disease, one that is exacerbated by dysfunction in adipose, liver, kidney, vasculature, and likely other organs. Emergent therapies for HFpEF modulate blood glucose levels; SGLT2 inhibitors act through the kidneys to reduce glucose reabsorption and thereby cause diuresis, reducing blood pressure. Furthermore, it is increasingly recognized that SGLT2 inhibition in cardiac cells, the vasculature, and systemically also contributes to the beneficial actions of these drugs in heart failure. A second emergent therapy for HFpEF is GLP1 agonism, which increases insulin secretion and depresses appetite, thereby decreasing body mass.[8] These drugs have powerful effects to improve the symptoms of HFpEF, including increased exercise capacity and reduced C-reactive protein levels.[9] A recent randomized clinical trial showed that semaglutide attenuated renal dysfunction, reduced major cardiovascular events, and reduced death in patients with kidney disease and type 2 diabetes,[10] further evidence of the multiorgan benefits of this therapy in HFpEF. Given the potential effectiveness of SGLT2 inhibitors and GLP1 agonists, it would be interesting to determine if these agents attenuate inflammatory signaling in HFpEF (in populations presenting with

this subphenotype) and whether they counteract the deleterious actions of ICAM-1 missense mutations. Randomized clinical trials of novel pharmacologic treatments for HFpEF, including anti-inflammatory drugs, SGLT2 inhibitors, or GLP1 agonists that directly test the impacts of these drugs alone, or in combination, across genetically distinct populations, have not been reported. Future translational studies of HFpEF need to address these observations head on. For instance, do genetic variation or environmental triggers that influence cardiac function also influence the other major symptoms of HFpEF in humans, namely, physical exhaustion and edema? In addition, future discovery-based approaches may examine the various tissues involved in HFpEF onset and pathogenesis, to determine cell type–specific reprogramming that leads to this multiorgan disease.

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ADDRESS FOR CORRESPONDENCE: Dr Thomas M. Vondriska, Departments of Anesthesiology & Perioperative Medicine, Physiology and Medicine, David Geffen School of Medicine, Molecular Biology Institute, University of California-Los Angeles, 650 Charles Young Drive, Los Angeles, California 90095, USA. E-mail: tvondriska@mednet.ucla.edu. OR Dr David J. Lefer, Department of Cardiac Surgery, Smidt Heart Institute, Cedars-Sinai Medical Center, 127 South San Vicente Boulevard Pavilion, Suite A3600, Los Angeles, California 90048, USA. E-mail: david.lefer@cshs.org.

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