Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.03.033

EDITORIAL COMMENT

Heart Failure Preserved Ejection Fraction With Coronary Artery Disease

Time for a New Classification?*

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In the past, systolic dysfunction was believed to be the predominant cause of heart failure (HF). That concept is no longer tenable, because in the United States and elsewhere, at least half of the HF population has a normal or near-normal left ventricular ejection fraction (LVEF). Even more striking is the observation that the percent of patients with heart failure with preserved ejection fraction (HFpEF) appears to be increasing in relation to the percent that have heart failure with reduced ejection fraction (HFrEF) (1).

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The reason for this shift in the ratio between HFpEF and HFrEF is related to differences in etiologies of these conditions. Although the underlying causes of HFpEF have yet to be fully delineated, changes in the diastolic properties of the heart that occur with aging are clearly involved (2). Thus, as the mean age of the population increases, HFpEF will become more common. In contrast, greater availability of therapeutic interventions that limit myocardial damage (particularly, in the setting of an acute myocardial infarction) should reduce the incidence of HFrEF. As a result, HFpEF will emerge as the predominant form of HF throughout the world in the not too distant future.

Over the past 5 decades, effective treatments for HFrEF have become available, and when used appropriately, they improve the clinical course of the disease. For patients with HFpEF, however, there has been little progress in developing new treatments, and no therapy to date has been shown to alter the natural history of the condition. Although the disparity in efficacy of treatments between HFrEF and HFpEF has many possible explanations, 1 critical factor is that drugs and devices that favorably alter outcomes in HFrEF patients are directed toward critical pathophysiological targets that are common in this study group. In contrast, identification of universally relevant targets in the HFpEF patient group has been elusive. The fact that strategies that have proven to be highly effective in treating HFrEF patients (e.g., neurohormonal blocking agents) have failed to produce similar favorable results in the HFpEF group indicates fundamental differences between these conditions.

The dichotomy in progress in developing treatments for HFrEF and HFpEF and the absence of a clearly definable common disease pathway for HFpEF suggest that heterogeneity in the underlying pathophysiological mechanisms strongly influence an individual patient's clinical course and their response to treatment. This theory further implies that by identifying a specific pathway that either results in the development of HFpEF or strongly influences the subsequent clinical course, therapeutic strategies that successfully correct the underlying abnormality would favorably affect the natural history of the disease. In this issue of *the Journal,* Hwang et al. (3) explore the implications of the presence of coronary artery disease (CAD) in HFpEF patients. Using the extensive Mayo clinic database, these investigators identified 376 HFpEF patients who underwent coronary angiography at their institution. They found that approximately two-thirds of these patients had CAD (defined as >50% stenosis). The patients with CAD had greater deterioration in ventricular function and increased mortality during follow-up compared with patients without significant coronary lesions. Moreover, the CAD patients who were revascularized (either percutaneously or surgically) had improved outcomes compared with patients who were not revascularized. These findings persisted even after adjusting for other variables that were likely to influence outcomes. The investigators concluded that the natural history of HFpEF patients with CAD differs from those without CAD, and that patients should be categorized on the basis of whether CAD is present.

Hwang et al. (3) are to be congratulated for their rigorous analysis. Their work should help focus attention on the issue of CAD in the HFpEF patient group and alert clinicians to the need to carefully assess their HFpEF patients for the presence and severity of CAD. The latter, however, may prove more difficult than imagined, because the investigators also reported that neither symptoms nor stress testing were highly predictive in this population. Overall, approximately one-third of HFpEF patients with and without CAD had angina symptoms, and both false negative and positive results from ischemia testing were common, even when the more stringent criteria of >70% stenosis was used for identifying significant CAD. The predictive values of both angina and stress testing in detecting CAD in a comparable non-HF study group from the investigator's institution would be of interest in trying to put these findings into context and to help determine whether making the diagnosis of CAD is really more difficult in HFpEF patients than in

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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other groups of elderly patients. The patients with CAD, however, did differ somewhat from the rest of the population in that they tended to be older, had more risk factors, were receiving more ischemic treatments, and in some cases, had undergone revascularization procedures. Although none of these parameters alone could be used to define the presence or absence of CAD, the cumulative profile indicates that clues in the patient's history can help clinicians decide whether or not to proceed with angiography or other tests to detect CAD in a HFpEF patient.

This current study is not the first to assess the prevalence and impact of CAD in HFpEF patients, and as noted by the investigators, the prevalence of CAD in their HFpEF patient group was higher than that in other surveys (1,4,5). This difference can be attributed to the requirement for coronary angiography for inclusion in the current analysis. Previous reports that did not systematically evaluate CAD, however, might have underestimated its prevalence in the patient groups studied. Nonetheless, the picture that emerges is that CAD is fairly common in HFpEF patients, and that its presence strongly influences the clinical course. There was significantly greater deterioration in LVEF in patients with CAD than in those without significant CAD, a finding that could be only partially explained by an intercurrent myocardial infarction. The mean reduction in LVEF (4.6 ± 10.3% in the CAD patients vs. 1.0 ± 8.7% in patients without CAD), however, did not appear to be of sufficient magnitude to explain the differences in clinical course that were observed in this study. The fact that follow-up LVEF measurements were obtained in only 218 of the 376 (58%) patients might have affected this result. Nonetheless, as shown in Figure 3 of the study by Hwang et al. (3), a substantially greater proportion of the CAD group experienced a reduction in LVEF to <0.50, and in some patients, this reduction was quite profound. In addition, the presence of significant CAD emerged as a significant risk factor for mortality, an effect that persisted in multivariate analysis that incorporated other univariate predictors. Although these results strongly supported an adverse impact of CAD on the clinical course of HFpEF patients, they provided little insight into the mechanism involved. In addition to an effect on systolic function, the potential mechanisms included the possibility that CAD predisposed patients to lethal ventricular arrhythmias or that it affected diastolic properties of the left ventricle by either directly impairing cardiomyocyte relaxation or by altering the amount (or composition) of the interstitial matrix of the heart.

The most intriguing (and problematic) aspect of this study was the information about the effects of revascularization on cardiac function and outcomes. Of the 255 HFpEF patients who were studied, 205 (80%) underwent revascularization done either percutaneously (63%) or surgically (37%). Repeat echocardiographic evaluation done on a subset of 60% of these patients showed a greater reduction in LVEF in patients who were not completely revascularized compared with those who were. In addition, the patients who were completely revascularized experienced significantly better survival than did patients who were not completely revascularized. Although these findings suggest a highly favorable and clinically relevant effect of revascularization in HFpEF patients with substantial CAD, it is important to note that there were no pre-defined criteria for intervention. Despite similarities in reported variables at the time of initial evaluation between patients who underwent revascularization and those who did not, the possibility of selection bias looms heavily over these findings. Thus, the role of revascularization in the HFpEF patient group remains uncertain, and recommendations for proceeding with either percutaneous or surgical intervention still must depend on existing guidelines for management of CAD, regardless of the presence of HFpEF.

So what are the implications of this study? The data help emphasize that although CAD is common in the HFpEF patient group, it is difficult to accurately detect by either symptoms or stress testing. Thus, new strategies are needed to help diagnose CAD in the HFpEF group. Although CAD appeared to adversely affect outcomes, the mechanism involved is far from certain, and further research to identify the mechanisms by which CAD alters the natural history of HFpEF is needed. Despite the encouraging results of the current study, further research is also needed to determine whether revascularization favorably affects outcomes in HFpEF patients and which segments (if any) of this rapidly growing elderly patient group with numerous co-morbid conditions would most likely benefit from either surgical or percutaneous interventions.

An argument for classifying HFpEF patients according to the presence of CAD can be made on the basis of the fact that CAD is common in this patient group; it appears to alter the clinical course, and it presents a therapeutic target for a disease for which no currently available treatments are known to affect long-term outcome. Uncertainty about the magnitude of the effect of CAD on outcomes, the mechanisms involved, and the lack of definitive evidence that revascularization alters the clinical course, however, suggests that a new taxonomy on the basis of the presence of CAD should be approached cautiously. Rather, as with hypertension or atrial fibrillation, both of which occur commonly in this study group, CAD should be considered an important co-morbidity that can affect the clinical course of HFpEF patients. This approach would help maintain focus on the HF component of the patient's illness without detracting from the need for diagnosing and treating CAD. It is worth noting that although testing for CAD is often rigorously pursued as part of the evaluation of HFrEF patients, this may not be the case in the HFpEF patient group. There is evidence that quality measures such as discharge instructions and control of blood pressure are less likely to be pursued in HFpEF compared with HFrEF patients, and that elderly HF patients (most of who have HFpEF) are less likely to see a cardiologist, have an echocardiogram performed, or even receive discharge counseling (6,7). Thus,

although greater attention to the presence of CAD in HFpEF patients is warranted, it appears that a substantial change in existing practice patterns would be required for this to occur.

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Key Words: coronary artery disease ■ diastolic heart failure ■ heart failure ■ heart failure with preserved ejection fraction ■ revascularization.