Rev Esp Cardiol. 2017;70(5):318–319

Editorial

Left Ventricular Ejection Fraction in Patients With Acute Heart Failure: A Limited Tool?

Fracción de eyección del ventrículo izquierdo de pacientes con insuficiencia cardiaca aguda: ¿un marcador débil?

Andreas P. Kalogeropoulos[a,*] and Javed Butler[b]

[a] Division of Cardiology, Department of Medicine, Emory University, Atlanta, Georgia, United States
[b] Division of Cardiology, Department of Medicine, Stony Brook University, Stony Brook, New York, United States

Article history:
Available online 7 January 2017

It is common to classify patients with either acute or chronic heart failure (HF) based on their left ventricular ejection fraction (LVEF) at presentation—both in clinical practice and in research studies, including practice-defining trials. Although this approach is rooted in the different pathophysiology of HF according to impairment of cardiac output at rest, it has some inherent limitations. First, the cutoff point to classify LVEF as reduced (HFrEF) or preserved (HFpEF) is necessarily arbitrary, ranging between 40% and 50% in the various studies. This has led the European Society of Cardiology to propose a new category of HF patients with LVEF values between 40% and 49%, termed HF with midrange ejection fraction (HFmrEF).[1] Second, a number of echocardiographic studies, both with the standard approach and with myocardial deformation imaging, have convincingly demonstrated that preserved LVEF does not guarantee preserved systolic function of the left ventricle.[2,3] In the TOPCAT trial, an echocardiographic study, 52% of patients had impaired global longitudinal strain, and this impairment was strongly associated with cardiovascular death and HF hospitalization.[3] In addition, patients with impaired global longitudinal strain seem to have benefited more from aldosterone antagonist therapy in a post hoc analysis.[3] Third, beyond the absolute value of LVEF at presentation, the trajectory of LVEF also has important clinical implications. In a recent large cohort study,[4] patients who presented with preserved LVEF as a result of improvement or recovery of HFrEF had a significantly better prognosis than patients with persistently reduced or preserved LVEF. The latter is especially important for patients with HFmrEF who frequently fall under this category. Finally, in contrast to HFrEF, in which low cardiac output and the resultant neurohormonal activation dominate the pathophysiological process, HFpEF, and by extension HFmrEF, have a more diverse pathophysiology and probably cannot be treated as a single phenotype for therapeutic and management purposes.[5] Clearly, despite the clinical utility and the prognostic significance of LVEF, especially among patients with HFrEF, the use of LVEF alone is problematic for clinical classification of HF, particularly for HFmrEF and HFpEF patients.

In a recently published article in *Revista Española de Cardiología*, Gómez-Otero et al. provide further evidence to question LVEF as the sole indicator of left ventricular function and overall HF status in patients with acute HF.[6] The authors investigated the baseline characteristics and outcomes of patients admitted with acute HFmrEF (40%-49%) in comparison with patients with acute HFrEF ($<$ 40%) and HFpEF ($\geq$ 50%), and observed that patients with HFmrEF share characteristics with both the HFrEF and the HFpEF groups. The clinical characteristics of the HFmrEF group were closer to those of the HFpEF group, but importantly, after 1 year of follow-up, there were no differences in total mortality, causes of death, and hospital readmissions for HF between the LVEF groups.

Several findings in this study merit further discussion—the most striking being the lack of prognostic significance of "acute" LVEF and the lack of prognostic discriminative ability of the newly proposed HFmrEF category. Similar findings, pointing to no or limited prognostic value of LVEF in acute HF, have been reported by other large registries.[7,8] As Gómez-Otero et al. point out, acutely measured LVEF is probably labile and may not reflect the actual cardiac status of a patient in the chronic state. In addition, the correlation of LVEF with hemodynamic, clinical, and neurohormonal measures is limited in patients with acute HF.[9] Beyond prognosis of mortality, another important finding is the lack of association between baseline LVEF and HF readmissions. Because readmissions for HF are not necessarily driven exclusively by disease biology,[10,11] it is unlikely that risk stratification based on LVEF alone would help us target patients who might benefit more from certain interventions to prevent readmissions. The study by Gómez-Otero et al. convincingly demonstrates this disconnect.

What are the clinical implications of the data presented by Gómez-Otero et al. from a HF management perspective in the acute and postdischarge settings? From a prognostic and immediate postdischarge perspective, these data imply that additional markers are needed to guide acute HF management. Indeed, as previously discussed, LVEF is probably a poor indicator not only of hemodynamics but also of systolic function in the acute phase, for a wide range of LVEF values. Biomarkers can potentially be used to further risk-stratify patients with HFmrEF, although this remains

SEE RELATED CONTENT:
http://dx.doi.org/10.1016/j.rec.2016.11.016, *Rev Esp Cardiol*. 2017;70:338–346.

* Corresponding author: Emory Clinical Cardiovascular Research Institute, 1462 Clifton Rd NE, Suite 535B, Atlanta, GA 30322, United States.
E-mail address: akaloge@emory.edu (A.P. Kalogeropoulos).

http://dx.doi.org/10.1016/j.rec.2016.11.029

to be evaluated in future research studies.[12] Because natriuretic peptide levels in HFmrEF patients demonstrate an intermediate range between HFrEF and HFpEF with a rather wide distribution and overlap with the other groups,[6] this approach seems to have considerable potential. On the other hand, natriuretic peptide-guided management has still to demonstrate definitive efficacy in patients with acute HF; however, the value of this approach might differ according to LVEF range and, in fact, preferentially benefit patients with HFrEF.[13,14] This might have implications for HFmrEF patients who are probably a mixed population from a left ventricle systolic function perspective. From a purely therapeutic angle, previous work has shown the presence of systolic dysfunction in preserved LVEF patients when assessed by advanced echocardiographic methods.[2,3] However, studies of neurohormonal blockade have not studied this group of patients to date—instead, patients with HFpEF, including HFmrEF in a number of studies, have been treated as a single entity. Considering the encouraging post hoc findings from the TOPCAT trial,[3] perhaps the time has come for a trial of neurohormonal blockade in HFpEF and HFmrEF patients with impaired systolic function, as expressed by impaired longitudinal systolic strain. In addition, it might be worth focusing on patients with an initial HFmrEF presentation, as patients who are recovering from HFrEF and present with midrange LVEF probably have a better prognosis and therefore it might be more challenging to demonstrate a beneficial effect with established or novel therapies in this group.

To date, there has been limited focus on patients with HFmrEF. The clinical characteristics of patients with HFmrEF, at least in the acute HF setting,[6] reveal a mixed patient population, potentially with different LVEF trajectories, and with outcomes similar to those of other acute HF groups. In the chronic HF setting, patients with recovering HFrEF as a result of response to guideline-recommended medications and device therapy probably have a better outlook than HFpEF patients who present with lower LVEF over time and become HFmrEF patients.[4] However, little is known about the latter group of HFmrEF patients because the LVEF trajectory has been reported by only a handful of studies. In addition, patients identified as HFmrEF during the acute HF setting may differ from chronic HFmrEF patients. Future longitudinal studies will need to evaluate prognosis and response to therapy in these important patient subgroups separately.

CONFLICTS OF INTEREST

A.P. Kalogeropoulos reports research support from the National Institutes of Health, the American Heart Association, the Centers for Disease Control and Prevention, the Atlanta Clinical and Translational Science Institute, and Critical Diagnostics. J. Butler reports research support from the National Institutes of Health, and European Union; and is a consultant to Amgen, Bayer, Cardiocell, Novartis, Boehringer Ingelheim, Trevena, Relypsa, Z Pharma, Pharmain, Merck, and Gilead.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37:2129–2200.
2. Kraigher-Krainer E, Shah AM, Gupta DK, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol.* 2014;63:447–456.
3. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation.* 2015;132:402–414.
4. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol.* 2016;1:510–518.
5. Butler J, Fonarow GC, Zile MR, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart Fail.* 2014;2:97–112.
6. Gómez-Otero I, Ferrero-Gregori A, Varela Román A, et al. Mid-range ejection fraction does not permit risk stratification among patients hospitalized for heart failure. *Rev Esp Cardiol.* 2017;70:338–346.
7. Coles AH, Tisminetzky M, Yarzebski J, et al. Magnitude of and prognostic factors associated with 1-year mortality after hospital discharge for acute decompensated heart failure based on ejection fraction findings. *J Am Heart Assoc.* 2015;4:e002303.
8. Senni M, Gavazzi A, Oliva F, et al. In-hospital and 1-year outcomes of acute heart failure patients according to presentation (de novo vs. worsening) and ejection fraction. Results from IN-HF Outcome Registry. *Int J Cardiol.* 2014;173:163–169.
9. Uriel N, Torre-Amione G, Milo O, et al. Echocardiographic ejection fraction in patients with acute heart failure: correlations with hemodynamic, clinical, and neurohormonal measures and short-term outcome. *Eur J Heart Fail.* 2005;7:815–819.
10. Allen LA, Smoyer Tomic KE, Smith DM, Wilson KL, Agodoa I. Rates and predictors of 30-day readmission among commercially insured and Medicaid-enrolled patients hospitalized with systolic heart failure. *Circ Heart Fail.* 2012;5:672–679.
11. Lu ML, Davila CD, Shah M, et al. Marital status and living condition as predictors of mortality and readmissions among African Americans with heart failure. *Int J Cardiol.* 2016;222:313–318.
12. Richards AM. Plasma neprilysin concentrations: a new prognostic marker in heart failure? *Rev Esp Cardiol.* 2015;68:1053–1055.
13. Brunner-La Rocca HP, Eurlings L, Richards AM, et al. Which heart failure patients profit from natriuretic peptide guided therapy?. A meta-analysis from individual patient data of randomized trials. *Eur J Heart Fail.* 2015;17:1252–1261.
14. Pascual Figal DA, Casademont J, Lobos JM, Piñera P, Bayes-Genis A, et al. Natriuretic peptides: consensus call for use. *Rev Esp Cardiol.* 2016;69:817–819.