ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2023) **24**, 301–303
https://doi.org/10.1093/ehjci/jeac268

EDITORIAL

The challenge of understanding heart failure with supernormal left ventricular ejection fraction: time for building the patient's 'digital twin'

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Online publish-ahead-of-print 13 January 2023

This editorial refers to 'Unfavourable outcomes in patients with heart failure with higher preserved left ventricular ejection fraction', by N. Ohte *et al.*, https://doi.org/10.1093/ehjci/jeac240.

The most widely used biomarker of left ventricular (LV) systolic function is ejection fraction (EF), and it is conventionally dichotomized into normal and reduced EF, with 50% as the lower limit of normal. Thus, heart failure (HF) was traditionally categorized as HFpEF or HFrEF when EF was preserved or reduced, respectively. More recently, a third category of mid-range EF between 40 and 50% was introduced. Such phenotyping of HF guides diagnosis and treatment via drugs and devices. However, EF has significant limitations as a single parameter for the assessment of ventricular function.

As shown by Wehner *et al.*,[1] in a study of over 200 000 patients referred for echocardiography with a median of 4 years of follow-up, there was a U-shaped relationship between EF and mortality, and the nadir was an EF of 60–65% (*Figure 1*). As expected, mortality increased progressively with a reduction in EF, but mortality also increased in patients with a supernormal EF. In fact, patients with EF ≥70% ($n = 13\,563$) had a similar adjusted mortality rate as patients with an EF of 35–40% ($n = 10\,595$). Furthermore, Saab *et al.*[2] showed in patients with acute coronary syndromes that EF >65% was associated with worse survival than an EF of 55–65%.

Ohte *et al.*[3] present data showing an unfavourable effect of high EF in patients with acute decompensated HF. This was a prospective multicentre cohort study of 255 patients admitted to hospital due to HF and discharged with EF >40%. The registry used for the study was primarily set up to assess the effects of β-blockers or angiotensin-converting enzyme inhibitors (ACEI). Patients were followed for an average of 522 days. The primary endpoint was a composite outcome of all-cause death and readmission due to HF, and the secondary endpoint was readmission due to HF. Seventy-three patients (28.6%) reached the primary endpoint. The study showed that a higher EF was associated with decreased event-free survival for both the primary and the secondary endpoints, regardless of β-blocker or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers usage. The discrimination threshold value for EF that could identify patients prone to reaching the primary endpoint was ≥57.2%. Furthermore, the study of Ohte *et al.* showed that LV end-systolic and end-diastolic volumes were markedly smaller in patients with EF ≥58% than with EF 40–58%.

Additionally, this study by Ohte *et al.* enhances the understanding of HFpEF pathophysiology by revealing in an acute HF population that a supernormal EF represents a risk factor. The observations that both LV end-diastolic and end-systolic volume were smaller in patients with a higher EF are consistent with typical HFpEF remodelling. Peak mitral early-diastolic velocity, tricuspid regurgitation pressure gradient, and left atrial volume index were all significantly higher in patients with EF ≥58% than in those with an EF of 40–58%, which is consistent with elevated LV filling pressure in the supernormal EF group.

Importantly, the study is limited by its moderate size and by the use of registry data from a study that was designed primarily to study the effect of HF drugs. Further validation of this finding is needed in a larger cohort with a wider range of EF, and myocardial strain analysis should be added.

Potential mechanisms of HF in patients with a supernormal EF were investigated in a recent study by Rosch *et al.*[4] They divided their HFpEF population into groups with EF 50–60 and >60%, and during afterload increase by isometric handgrip exercise, there were strikingly different haemodynamic responses in these subpopulations. Patients with an EF within 50–60%, responded with an elevation of LV filling pressure and an increase in end-diastolic volume. Patients with an EF >60% had smaller ventricles and showed an elevation of LV filling pressure, but without an increase in end-diastolic volume—consistent with higher diastolic stiffness—and there was a marked decrease in stroke volume and thus EF. The EF >60% group also showed a higher LV contractility (end-systolic elastance), which was coupled with a higher effective arterial elastance.

As shown by Kawaguchi *et al.*,[5] having normal or even supernormal EF does not always imply normal systolic function. It was found that patients with HFpEF had abnormal LV systolic stiffening, combined with arterial stiffening. When the myocardium is pumping blood into stiff arteries, it implies increased myocardial oxygen demand due to a higher

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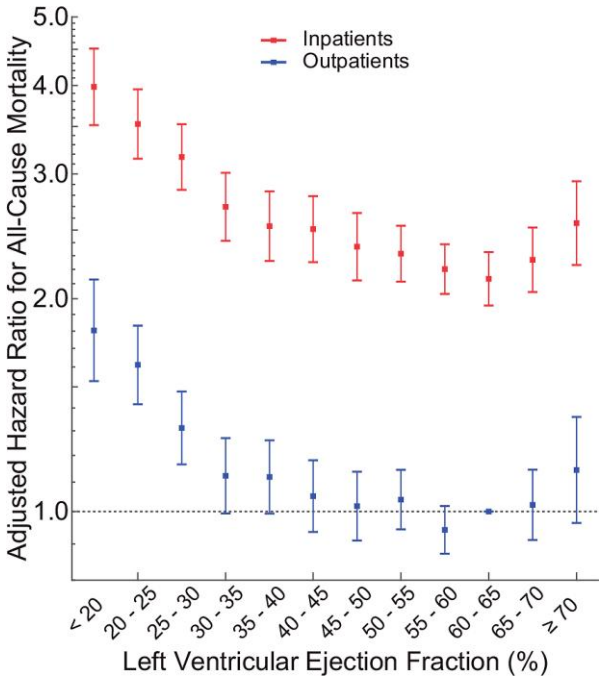

Figure 1 LVEF-adjusted hazard ratios in patients with heart failure (number of echocardiograms: 40 616).[1]

afterload, which acts as a stimulus for LV remodelling and diastolic stiffening.

In cardiomyopathies such as hypertrophic cardiomyopathy, cardiac amyloidosis, Fabry, and several others, there are structural changes that explain why supernormal EF and systolic dysfunction may coexist. The systolic dysfunction is reflected in a small stroke volume and reduced systolic global longitudinal strain (GLS). In these hearts, with a thickened LV wall at the cost of LV cavity volume, a minor myocardial contraction closes the chamber almost completely, which explains the existence of a supernormal EF in a failing heart.

However, these cardiomyopathies are relatively rare, and unlikely to be the driving mechanism to explain the association between a supernormal EF and cardiovascular risk observed in large patient populations. Arterial hypertension is a common comorbidity in HFpEF, causing compensatory LV hypertrophy with concentric remodelling, leading to worse outcomes.[6] Normal ageing is also associated with increasing LV systolic pressure and arterial stiffening, both leading to LV remodelling. As shown in a large cohort of individuals free of cardiovascular disease at baseline, ageing was associated with a progressive increase in EF, along with a reduction in end-diastolic volume and an increased LV mass-to-volume ratio, and in these ventricles, myocardial strain indicated systolic and diastolic dysfunction.[7] To what extent age-dependent LV remodelling and arterial stiffening explain the risk associated with supernormal EF remains to be determined.

In patients suspected of HFpEF, it is recommended to measure LV GLS as a supplementary parameter, due to a greater sensitivity than EF for diagnosing systolic dysfunction.[6] This is because EF reflects predominantly LV circumferential shortening, whereas GLS measures longitudinal shortening.[8] Because myofibres that account for longitudinal shortening are mainly located in the vulnerable subendocardium, a reduction in GLS often precedes a reduction in EF. Therefore, GLS is well suited as a supplementary measure in patients with supernormal EF to confirm systolic dysfunction.

In summary, the U-shaped relationship between EF and cardiovascular risk further extends the list of reasons why EF should not be used as a stand-alone measure of LV function. When supernormal EF is measured in hearts with thickened LV walls and small cavities, it should not be interpreted as increased contractility. LV GLS should be measured and may reveal systolic dysfunction. Future studies should explore if novel multimodality imaging can identify subgroups that better defines cardiovascular risk within the supernormal EF phenotype.

The goal is to elucidate in each heart failure patient the contributors to an increased afterload, increased diastolic and systolic stiffness, and in some cases, increased contractility. The key to unlock the management of the supernormal EF phenotype is to establish the relative importance of these contributors, e.g. through their integration into a computational model and systematic simulation to build the 'digital twin' of a patient.[9]

Conflict of interest: O.A.S. is a co-inventor of 'Method for myocardial segment work analysis' and has received one speaker honorarium from GE Healthcare. O.A.S. and J.F.F. have filed patents on 'Estimation of blood pressure in the heart'. P.L. sits at the scientific advisory board of Ultromics (Oxford, UK).

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