Heterogeneity of patients phenotyped as heart failure with mildly reduced ejection fraction

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Background: Current phenotyping of heart failure (HF) is based on the ejection fraction (EF) criterion, resulting into three types including the mildly reduced (mr) category. Little is known about the heterogeneity of the volumetric (ie left ventricular [LV] size) and clinical characteristics (including myocardial oxygen consumption, MVO₂) of patients who are assigned to the HFmrEF class.

Method: The metric EF combines details on end-systolic volume index (ESVi) and end-diastolic volume index (EDVi). Both volumetric measures can be presented in the volume regulation graph (VRG), allowing the graphical inspection of the behavior of EF under a variety of conditions, with stratification options based on age, sex or other clinically relevant determinants. To overcome the limitations intrinsic to ratio-based metrics such as EF, we introduced a logical EF-companion (EFCi), defined as the square root of (ESVi² + EDVi²). In other studies the EFCi has been shown to offer incremental value beyond the single use of EF.

Patients: LV volumes were determined by biplane angiocardiography in 190 HF patients (69 women), and retrospectively analyzed.

Results: Average ESVi values for mrEF are 57.9 and 60.2 mL/m² for men (n = 22) and women (n = 10), respectively. The distribution of (EDVi, ESVi) data pairs in the VRG is shown in Figure 1, stratified for women and men. Patients categorized as HFmrEF are indicated by separate markers, and located in the region between the lines that indicate the 40 and 50% limits for EF. The double arrowed yellow bar refers to the wide ESVi range (27 to 118 mL/m²) for the patients within this narrow EF bandwidth. As ESVi refers to the extent of (reverse) remodeling and is associated with MVO₂, there is a clear need the consider ESVi or EFCi for patients, in addition to their nearly similar EF values. Figure 2 shows the distribution of EFCi (range 59.5 to 231.8 mL/m²) for all HFmrEF patients, and clearly illustrates the supplementary value of the companion to the ratio-based metric EF.

Conclusions: As the bandwidth for EF narrows, the specificity of EF decreases and the higher the need to rely on EFCi. Thus, in contrast to the current view indicating that HFmrEF patients form a well-defined rather homogeneous phenotype exhibiting comparable clinically relevant characteristics, we found a relatively pronounced heterogeneity within the HFmrEF phenotype group. Distinguishing individual patients within the HFmrEF phenotype can be realized by considering the newly introduced parameter EFCi. This approach resolves most of the criticism thus far expressed regarding limitations of EF. The proposed additional dimension beyond EF offers a more comprehensive description of these patients, and will allow a personalized analysis based on a more careful characterization. Further investigations are warranted to explore implications for patient management.
Figure 1. VRG for HF patients (n = 190)

Figure 2. HFmrEF vs EFCi (n = 32)