Title: Redefining heart failure phenotypes based on ejection fraction.

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The authors of the European Society of Cardiology 2016 guidelines on the diagnosis and treatment of acute and chronic heart failure described a new term to categorise patients with a resting left ventricular ejection fraction (LVEF) in the range 40-49%, so called heart failure with mid-range ejection fraction (HFmrEF), formerly referred to as “grey-area” EF in the previous iteration of the guidelines.[1,2] This designation overlapped with the previously described heart failure with preserved ejection fraction (HFpEF) which had included patients with a LVEF >40% in one clinical trial but, more generally, patients with a LVEF >45%.[3–6] Puzzlingly, the 2016 guideline authors continued to use the description HFpEF for patients with a LVEF ≥50%. This change in terminology has caused understandable confusion and should be replaced.

So what is the problem? The description HFpEF entered common parlance when used by investigators in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Programme to describe the group of patients enrolled in one of the three component trials.[7] The word “preserved” was deliberately chosen to identify patients with a LVEF value that was not clearly “reduced” or completely “normal”. Subsequent trials have more commonly used a higher LVEF cut-point to identify patients with a “preserved” LVEF, usually 45% or above, primarily to ensure exclusion of patient with clearly reduced LVEF (given the variability around measurement of LVEF).[3,4,8]

There has also been uncertainty about what constitutes a “normal” LVEF value. The basis of many “reference ranges” is historical, generally lost in the mists of time. Fortunately, a large international collaboration has led to the pooling of individual-person data from 43 globally representative, population-based, echocardiography studies, allowing for the first time the development true age-, sex- and racially/ethnically appropriate adult reference values for LVEF.[9] Interestingly, if the fifth percentile is used as the lower reference value, then “normal” in an older man of European ancestry is 50% and that in an older European woman 51% (these values are higher in Asian men and women). These normative values are in keeping with those advocated by the joint European Association of Cardiovascular imaging and the American Association of Echocardiography guidelines on chamber quantification.[10]

Another confusing aspect of the ESC categorization of HF relates to the interpretation of LVEF measured using different imaging modalities. Normative values, based upon over 800 healthy volunteers, have recently been published for cardiac magnetic resonance (CMR) imaging, the gold standard assessment of cardiac volumes and LVEF.[11] This study reported normative values for LVEF in Caucasian men and women of ≥ 48 and 51%, respectively. Although these results are similar to the normative echocardiographic results described above, there is poor agreement comparing LVEF by echocardiography with that of CMR, with limits of agreement of -18.1% to 8.3% reported.[12] Added to this, two-dimensional (2D) echocardiography has an inter- and intra-operator variability of up to 15% and 10% respectively.[13] As a result, a patient with "HFmrEF" could in theory be categorized as any of the three HF phenotypes, depending on the imaging modality used. Indeed, the same patient could be assigned a diagnosis of HFpEF, HFmrEF or HFrEF within an hour if they were imaged by different individuals or by different modalities. The high inter- and intra-operator variability of 2D echocardiography can be reduced, substantially, by using contrast (and there is less variability with CMR).[11] This combination of high variability of 2D echocardiography derived EF and narrow EF range of HFmREF is one of the reasons why the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand have not adopted HFmrEF into their recently published HF guidelines, but have instead opted to keep a dichotomous classification of HF with HFrEF defined as an EF <50% and HFpEF as an EF ≥50%.[14]

How should we use these new data to refine our categorization of heart failure by LVEF? There are two options. The first would be to revert to two phenotypes (HFrEF and HFpEF). This, by definition, means that the designation "HFpEF" includes both patients with heart failure and a "normal" LVEF (HFnEF), as well as patients in the "grey area" 40-49% (for Europeans) – what in the 2016 ESC guidelines was defined as HFmrEF. This is what was originally intended by the term HFpEF. Although this two-category system would still be prone to potential misdiagnosis using 2D echocardiography as described above. The alternative is to have three categories: HFrEF, HFmrEF and HFnEF, with "normal" appropriately defined according to age, sex and race/ethnicity. Clearly the latter (three categories)

is operationally more difficult to employ than the former (two categories), although patho-physiologically more appealing. Indeed, the discussion, debate and analyses which followed the introduction of the term HFmrEF has indicated that at least some patients in this category seem to respond favourably to treatments for patients with a low LVEF whereas those with a clearly “normal” LVEF do not.[15–17] An arbitrary simplification of the 3 category solution might be to designate HFrEF as <40%, HFmrEF 40-54% and HFnEF as ≥55%.

Regardless of the classification system used, patients with an LVEF which is neither very obviously reduced or normal, should have this measured as accurately as possible, using either contrast echocardiography or CMR, to avoid under-diagnosis and under-treatment of HFrEF. Whichever of these options is preferred, it is wrong, at least in people of European descent, to describe patients with a LVEF ≥50% as having “preserved” LVEF – for men and most women ≥50% is normal.

Declaration of interest

None declared.

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