Ejection Fraction
Misunderstood and Overrated (Changing the Paradigm in Categorizing Heart Failure)

The long-standing emphasis on ejection fraction (EF) is misguided. EF is erroneously assumed to be a measure of myocardial contractility. Of greater concern is the widespread classification of patients with heart failure (HF) based on whether EF is preserved (HFrEF) or reduced (HFrEF). In fact, EF does not provide any specific information on causation or underlying mechanisms. We believe that a revision or abandonment of this nomenclature is warranted, and categorization of patients with HF should more strongly emphasize underlying pathophysiology.

WHAT EF REPRESENTS

EF is a characterization of ventricular ejection: the stroke volume (SV) expressed as a fraction of end-diastolic volume (EDV). Knowledge of EDV is essential to translate SV expressed as a percentage (EF) into absolute SV, a quantity of more physiological and clinical significance, hence our admonition that no one should ever mention EF without, in the same breath, diastolic volume.

In the 1950s, physiologists used the instantaneous change in SV/EDV (ie, the change in EF) as a measure of change in contractility under conditions of constant load. Over time we have largely forgotten that (1) EF is influenced by both preload (diastolic) and afterload (systolic) and cannot be interpreted as an index of contractility without knowledge of left ventricular (LV) loads; and (2) structural changes leading to increases or decreases in LVEDV will strongly influence the EF at a given level of contractility and SV. So EF is twice removed from an index of contractility and has little meaning on its own.

FACTORS ALTERING EF

Figure portrays schematics of P-V curves selected to represent the uncoupling of EF from contractility. Panels A and B represent changes in preload and afterload, respectively, in a normal heart. Panels C and D represent cardiac remodeling in HF with cardiac hypertrophy (C) and dilated cardiomyopathy (D). All panels include the same control P-V loop (in black) showing a 50 mL SV and 50% EF. In panel A, the P-V loop (in red) shows an increased EDV (preload), which increases SV and contractile force by the Frank-Starling mechanism, yet EF is barely changed (52%). In panel B, the increased vascular resistance (afterload) increases arterial pressure and contractile force (Anrep Effect), maintaining SV and increasing stroke work, yet EF is again barely changed (48%).

Panels C and D represent cardiac remodeling in HF, with decreases in myocardial contractility and in both SV and EF. Although SV is equally reduced to 25 mls in panels C and D and cardiac output may also be equally decreased, EF is significantly lower in dilated cardiomyopathy (19%) because of the larger EDV compared with hy-
pertrophic cardiomyopathy (28%), which encroaches on the LV cavity in diastole and reduces EDV. In patients with hypertrophic cardiomyopathy, EF may increase through remodeling and reduced ventricular cavity volume rather than increased SV or contractility.

In these examples, increased preload and afterload increase contractile force, yet EF is essentially unchanged. Conversely, in hypertrophic versus dilated cardiomyopathy, the decreases in SV, cardiac output, and myocardial contractility may be similar, yet EF is lower in dilated cardiomyopathy through structural remodeling, causing a larger EDV.

**VENTRICULAR VOLUMES, EF, AND CARDIAC REMODELING**

A structural change in LV volume is a dominant determinant of EF. The term “remodeling” arose to describe structural changes, first described in the 1970s, occurring after a large myocardial infarction. Scarring and thinning of infarcted myocardium and myocyte hypertrophy with interstitial fibrosis in the noninfarcted myocardium drive increases in EDV, with similar changes occurring in dilated cardiomyopathy. The term remodeling may also apply to cardiac concentric hypertrophy and fibrosis without dilatation, often in response to a chronic increase in afterload, as seen in hypertension and aortic stenosis. Similar remodeling may also be caused by a myocardial process, often associated with elements of the metabolic syndrome (diabetes mellitus, obesity, hyperlipidemia, and hypertension) and advanced age.

Each of the previously mentioned conditions is generally characterized by reduced myocyte contractility and lusitropy. However, EF change may not reflect contractility as much as it reflects ventricular remodeling. (Strain measurements may provide more meaningful information regarding contractility.) Although in patients with reduced EF, inotropes may acutely improve symptoms, these agents may worsen the underlying disease process and increase mortality. In contrast, neurohumoral and vasoactive interventions that reverse remodeling also reduce mortality.

**INACCURETE USE OF EF TO DISTINGUISH SYSTOLIC AND DIASTOLIC DYSFUNCTION**

Pathological hypertrophy and fibrosis, occurring in most patients with HF, are associated with abnormal contractility and relaxation. It is a misconception that reduced EF equates with systolic dysfunction and preserved EF with diastolic dysfunction. Even more unfortunate has been primarily using EF to classify patients with HF in clinical trial design. Because inotropes were explored to augment contractility in patients with HFrEF, calcium channel blockers were investigated to augment relaxation in patients with HFpEF. It was not recognized that the nature of remodeling—with or without LV dilation—was the primary driver toward reduced versus preserved EF. Assuming that EF defines the underlying disease mechanism has resulted in numerous neutral and inconclusive clinical trials.

**SHOULD THE METABOLIC SYNDROME BE DEFINED AS A SPECIFIC FORM OF HFPEF?**

The metabolic syndrome drives a process, perhaps accelerating one often seen in the elderly, leading to a form of HF with preserved EF with specific characteristics. The pathological process is one of tissue oxidation and inflammation, leading to myocardial fibrosis and hypertrophy as well as renal and vascular pathology. This disease state, which we may call metabolic-senile cardiovascular disease, should not be labeled HFpEF but characterized specifically as HF with nonenlarged LVEDV, concentric myocardial hypertrophy and fibrosis, abnormal LV relaxation and compliance, left atrial enlargement, and elements of the metabolic syndrome and advanced age in the absence of myocardial or pericardial infiltrative disease.
CONCLUSIONS

LVEF has exhausted its usefulness as a presumed marker of contractility and a means of categorizing cardiomyopathies. In fact, the latter practice has stymied advances in pathophysiological understanding and therapeutics. Underlying disease states may cross arbitrary EF boundaries, and multiple diseases may cause HF within any particular EF range. It’s time for a new paradigm. The descriptive term HFpEF is clinically and therapeutically useless. The term metabolic-senile cardiovascular disease distinguishes a circumscribed disease and pathological process, beginning before the clinical expression of HF, which should more aptly direct future therapeutic investigations. LV volume measurement is useful in assessing SV and characterizing LV remodeling, but let’s focus on the underlying disease in considering novel therapies.

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