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EDITORIAL

Insights from physiology applied to interpretation of supranormal ejection fraction in women

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This editorial refers to 'Increased long-term mortality in women with high left ventricular ejection fraction: data from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) long-term registry', by C. Gebhard *et al.*, pp. 363–374.

> *. . . it is of clinical importance to know when the heart is disproportionally small*
>
> Bardeen (1918)[1]

Traditionally, attention has been given to cardiac enlargement, but less is known about relatively small hearts. This imbalance may result from emphasis on the Starling mechanism, relating output to extent of filling. Actually, ejection fraction (EF) follows from this relationship, where stroke volume (SV) is compared to end-diastolic volume (EDV). EF is a dimensionless number, often expressed as a percentage, and calculated from paired volume determinations, namely end-systolic volume (ESV) and EDV. A *PubMed* search on EF refers to >62 000 publications since 1968.[2] In view of the popularity, it is important to inquire about the applicability and interpretation of EF.

Based on the CONFIRM registry, Gebhard *et al.*[3] report on excess long-term mortality in women with a hyperdynamic left ventricle (LV). Their initiative to explore both ESV and EF to characterize sex-specific subgroups is a welcome step forward.[4–6] By adding insight based on physiology, our commentary addresses the connection between EF and ESV,[4,5] provides the rationale for a preference in favour of ESV,[6] and discusses energetic aspects of 'supranormal' EF.

Keen observations by Buonanno[7] revealed important sex-specific differences regarding LV size. This pioneer highlighted the hyperactive LV in healthy women compared to men and suggested that *the combination of an increased EF and small LV volume reflects a hyperdynamic condition with increased metabolic demand*. Supranormal EF as a pathological finding was probably first reported by Kahn,[8] considering EF >85%. The entity not only occurs in disease-free women[7] but also in patients, e.g. with phaeochromocytoma or severe anaemia, and is equivocally defined in terms of EF threshold. The distinction between the commonly encountered label 'supranormal' and the variant 'high normal'[3] is of a trivial semantic nature, as both refer to hyperdynamic states.

What has EF to do with ESV? By definition EF = 1 – (ESV/EDV). As EF depends on two components within a ratio, its interpretation involves a mathematical exercise concerning the relative impact of the numerator and denominator.[4,6] In case of EF, the analytical expression which connects with ESV is remarkably simple. The use of two population-based constants permits formulation of EF as an exclusive nonlinear function of ESV.[5,6,9,10] Alternatively, a convenient logarithmic approach can be applied.[11] Both routes yield an inverse relationship. *Figure 1* shows EF = SV/(ESV + SV) for sex-dependent average SV from Gebhard *et al.*[3] The non-linearity illustrates that EF increases disproportionally at smaller ESV. This finding is crucial when elucidating their results. Also, differences observed between men and women deserve close inspection.

The LV is said to perform poorly at low EF values. While searching for an optimal EF, a connection has been made with the golden ratio which refers to the irrational number φ, often observed in nature.[6] The numerical value of φ, 1.618, is a convenient approximation. Its reciprocal in fact comes remarkably close to a 'normal fraction' for EF (which depends on imaging modality used) as observed in healthy individuals.[4,6] The appealing role of this number is supported by allometry, leading to similar values for healthy adults of all mammalian species.[13] Nature appears to dictate in healthy individuals an optimal value for ESV and EDV, and hence for EF. On energetic grounds this ESV value coincides with lowest cardiac oxygen consumption.[9] Relatively small ESV corresponds with low efficiency, much like the enormous effort required to squeeze out the last few drops of fluid from a wet sponge. The elastance concept suggests a 'swoosh'-

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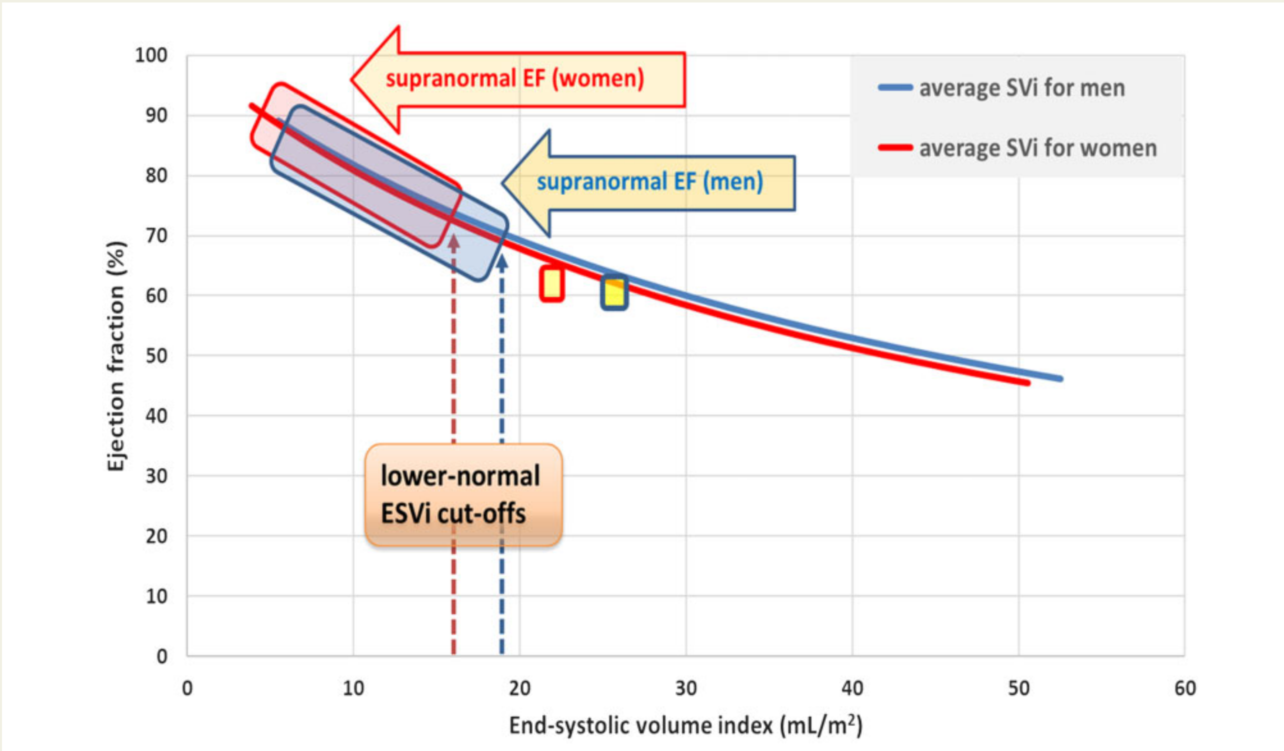

Figure 1 Schematic visualization of ejection fraction (EF) vs. end-systolic volume index (ESVi), based on sex-specific average data from Gebhard *et al.*[3] Supranormal EF regions refer to sex-specific cut-offs for ESVi.[3,12] Squares mark group averages.[3] Curves for additional patient groups are documented elsewhere.[4–6,9–11]

shaped curve for myocardial oxygen consumption vs. ESV (*Figure 2*).[9] The study by Gebhard *et al.*[3] specifically addresses one leg of this curve, namely the one for small ESV, with cut-offs adopted from Petersen *et al.*[12] Actually, another CONFIRM publication supports this model on the opposite side of the spectrum, documenting better survival for ESV < vs. ≥ 90 mL for the LV.[14] Data points are shifted because women tend to have smaller ESV levels, even after indexation (i) for body surface area (*Figure 1*), compared to their matched male counterparts.[3,4,6,7,9,10,15]

Gebhard *et al.*[3] focused on 'small hearts' (i.e. LVESV < 25 mL) and 'high normal EF'. Based on the energetics principle outlined here, it is evident that it is due to the smallness of such LVs that problems arise. A relatively tiny ventricle can only pump sufficient blood (SVi in *Figure 1*) when operating in hyperdynamic mode. This abnormal state requires more oxygen to do the same work and likely contributes to increased long-term mortality. Their study is a tribute to the pioneering work of Buonanno,[7] and shifts exclusive focus away from the metric EF[6,15] towards the more robust and physiologically relevant variable ESV.[5,9,10] The fact that curves in *Figure 1* converge to the supranormal EF range for small values of ESV, is the major reason why EF and ESV provide comparable information, but *only* in that particular region.

The observation that higher EF values (*Figure 1*) are more abundant in women ($P = 0.002$ for EF > 70%)[3] follows from their tendency to have a relatively smaller ESV ($P < 0.001$ for ESV < 25 mL)[3] compared to men, also in general.[4,9–11] The precise extent depends on all factors which govern LV volume regulation, being modulated by age,

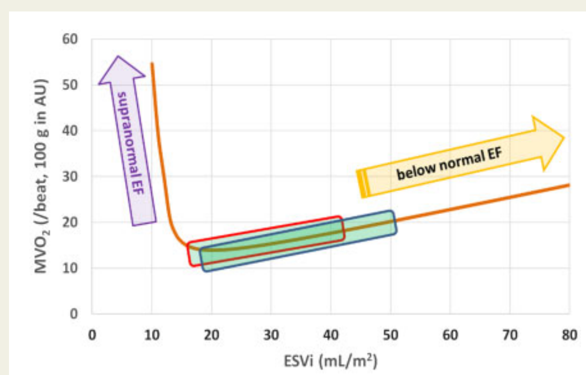

Figure 2 Energetic considerations based on the systolic elastance concept[9] permit prediction of myocardial oxygen consumption (MVO_2).[9] Nadir near an 'archetypal' (i.e. energetically optimal) end-systolic volume index (ESVi). Red outlines the range for 'normal EF' women, blue for men.[3] AU, arbitrary unit.

comorbidities, severity of coronary epicardial artery, and microvascular disease, plus other variables. Gebhard *et al.*[3] did not specify potential confounders, such as haemoglobin level or interfering medication use nor thyroid status. Ideally, such clinically relevant details should be incorporated.

Interpretation of EF is more difficult than its calculation. EF is a complex metric, apart from being incomplete,[6,15] and ESV deserves preference.[5,9,10,15] Bardeen[1] and Buonanno[7] demonstrated that LV size and sex matter. These notions are further explored by Gebhard *et al*. in patients evaluated for coronary artery disease.[3]

Conflict of interest: none declared.

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