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What is preserved LV ejection fraction in aortic stenosis: 0.50, 0.55 or 0.60?

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Introduction

Just as the lines defining cut-offs for the diagnosis of hypertension and hyperlipidaemia are arbitrary divisions of continuously distributed variables (blood pressure (BP), plasma lipids), the line separating 'preserved' from impaired LV function is also an arbitrary one. It is a point of convenience – a starting point on which decisions to act can be based – above which, risk (in the form of clinical endpoints) accrues significantly more quickly, although not exclusively. The most appropriate threshold separating preserved from impaired LV function will depend on the substrate in question (acute and chronic haemodynamic loading conditions, contractility and inotropic status, heart rhythm and rate), the subject's age and sex, the measured parameter (e.g. ejection fraction (EF), fractional shortening, global longitudinal strain (GLS), MAPSE, stroke work), and modality (e.g. echocardiography, cardiac magnetic resonance (CMR), radionuclide ventriculography). This can be difficult to judge. In borderline cases or where there is mixed valvular heart disease, previous measurements can be particularly helpful to assess what is 'normal' for that individual.

As a starting point then, preserved LV function is a slippery concept if

Take Home Messages

- Symptoms or LV dysfunction, defined as LVEF < 0.50, are class I indications for intervention in severe AS. But ~30% of subjects with asymptomatic severe AS have LVEF 0.50-0.59, a level that overlaps with 'normal LVEF' in the absence of valvular heart disease.
- At the time of diagnosis of asymptomatic severe AS, LVEF 0.50-0.59 predicts increased all-cause mortality compared with LVEF ≥ 0.60 (2 of 3 studies reviewed here).
- In the presence of moderate AS, LVEF 0.50-0.59 predicts having LVEF < 0.50 at time of diagnosis of severe AS, with the downward trajectory being fastest at AVA <1.2 cm^2.
- These observational studies indicate that there is a subset of pressure-overload intolerant ventricles which in the presence of moderate or severe AS display LVEFs 0.50-0.59 – these ventricles may benefit from a higher LVEF cut-off for intervention, but the strategy lacks randomized supporting evidence and one would have to stringently avoid patient-prosthesis mismatch.

unqualified. To make things worse, we do not measure it multiple times daily, as we do blood pressure. EF has become the most widely used indicator of systolic function, partly because of its ease of understandability (across specialties) and applicability (across vendors and modalities). LVEF is a good example of a continuous variable dichotomized into values that we accept connote higher risk and values we may falsely feel reassured about [1,2]. Reference ranges (mean ± 2 SD) for normal LVEF by Simpson's biplane 2D echocardiography were recently updated from ≥ 0.55 [3] to 0.52—0.72 (men), 0.54—0.74 (women) [4], and ≥ 0.52 (men), ≥ 0.54 (women) [5]. By comparison, normal LVEF ranges (mean ± 2 SD) are higher by steady-state free precession (SSFP) CMR at 1.5T: 0.57—0.75 (men, age < 60), 0.59—0.77 (men, age ≥ 60), 0.58—0.76 (women, age <60), and 0.60—0.78 (women, age ≥ 60) [6]. Despite marginally higher reference LVEFs at 3T, a consistent finding is that LV volumes tend to decrease with age [7].

Despite the dependency of echo-derived LVEF on operator and acoustic window, and despite its relative insensitivity for detecting early myocardial dysfunction when compared with measures such as GLS [8] or brain natriuretic peptide, disease- and indication-specific cut-offs for abnormal LVEF as ascertained by Simpson's biplane 2D echocardiography are widely trusted: in heart failure, where LVEF cut-offs separate preserved, mid-range and reduced EF heart failure (LVEF ≥ 0.50, 0.40-0.49, and < 0.40) [9], before intracardiac device implantation for primary prevention of sudden cardiac death (LVEF ≤ 0.35) [10], and in valvular heart disease, where the management of asymptomatic severe valve disease remains debated. In asymptomatic severe chronic primary mitral regurgitation, an LVEF ≤ 0.60 and/or LVESD ≥ 45 mm predict worse postoperative outcome independent of symptom status, so are indications for surgery (Class IB) [11]. In asymptomatic severe chronic aortic regurgitation, an LVEF ≤ 0.50 in the absence of another cause warrants surgical repair (class IB indication), while in asymptomatic severe aortic stenosis (AS), an LVEF < 0.50 defines systolic LV dysfunction and in the absence of another cause warrants surgical AVR (class IC indication) [11]. Considering that increased afterload and systolic wall stress tend to depress LVEF and that reduced afterload and increased preload tend to flatter LVEF – all other factors fixed – these seem to be reasonable thresholds.

Subjects with low-flow low-gradient severe AS (AVA < 1.0 cm^2, mean gradient < 40, stroke volume index < 35 ml/m^2) with low LVEF (≤ 0.40) are uncommon, comprising 5-10% of subjects with severe AS [12], and have a poor prognosis [13–17]. Some 20% of newly diagnosed subjects with severe AS have LVEF < 0.50 [18]. In the presence of moderate AS also, LVEF < 0.50 carries a poor prognosis [19]. Subjects with asymptomatic severe AS and LVEF < 0.50 at diagnosis are even more uncommon, with one study of 9940 adults ≥ age 40 with severe AS documenting a prevalence of 0.4% and five-year mortality of 48% [18]. At odds with current guidelines, which define the presence of LV dysfunction in severe

AS as LVEF < 0.50, three observational natural history studies published in 2018, all using the Simpson biplane method, have raised the question of whether this threshold is too conservative. A substantial minority (31%) of subjects with asymptomatic severe AS have an LVEF in the range 0.50-0.59 [20]. All three studies (reviewed below) call attention to the increased mid-term overall mortality risk conferred to this borderline group, as compared with subjects with LVEF ≥ 0.60. Thus current guidelines may fail to recognise that a substantial minority of subjects with asymptomatic AS, previously regarded as unremarkable, in fact carry a worse prognosis than conventionally appreciated.

Study one

In the first, a single-centre retrospective cohort study from Mayo Clinic, Rochester, Minnesota, USA, the authors attempted to understand the association between LVEF and aortic valve area (AVA) over time by using serial echocardiography in subjects identified with a first diagnosis of severe AS (time zero) and at least one echocardiogram within the preceding ten years [21]. Exclusion criteria were severe aortic or mitral regurgitation, previous valve surgery, dilated cardiomyopathy, active endocarditis or prior radiotherapy. 928 patients (mean age 78) with a median three echocardiograms prior to the time zero echocardiogram were included, and at time zero were divided into two groups: LVEF < 0.50 (n = 196) and LVEF ≥ 0.50 (n = 732).

Subjects with LVEF < 0.50 were more likely to have atrial fibrillation or flutter, LBBB, coronary artery disease (CAD), prior myocardial infarction (MI), and higher NT-proBNP. When the timepoints –3 ± 1 years and time zero were compared, the group with LVEF < 0.50 at time zero had displayed a gradual and significant decline in LVEF, from 0.498 ± 0.129 (mean ± SD) to 0.354 ± 0.098, while the group with LVEF ≥ 0.50 did not (from 0.642 ± 0.065 to 0.642 ± 0.058). The rate of decline accelerated at -1 year in the impaired LVEF group only, at which point mean AVA across both groups was 1.2 cm^2. Comparing the groups at –3 years, the group with LVEF < 0.50 at time zero had larger LV end-diastolic and end-systolic diameters (LVEDD 53.0 ± 6.3 vs 47.9 ± 5.2 mm, p < .001, LVESD 38.9 ± 8.1 vs 29.8 ± 4.6 mm, p < .001) and lower concentricity (relative wall thickness[1] 0.42 ± 0.07 vs 0.47 ± 0.09, p < .001).

On multivariable logistic regression controlling for age, atrial fibrillation/flutter and CAD, independent predictors (at time -3 years) of LVEF < 0.50 at time zero were male sex (odds ratio 2.84, 95% CI 1.52-5.49), LVEF (OR 0.86, 95% CI 0.83-0.89), log medial e' (OR 0.34, 95% CI 0.13-0.85), bicuspid aortic valve (OR 0.15,

[1] Relative wall thickness (RWT) = 2 x posterior wall thickness / LVEDD. Normal range is 0.32-0.42. Values > 0.42 indicate concentric remodelling or hypertrophy [25].

95% CI 0.02-0.59), and LBBB (OR 3.66, 95% CI 1.79-7.47). Cut-off values for LVEF at -3 years that would best predict LVEF < 0.50 at time zero were calculated using receiver-operating characteristic (ROC) curves: the best value for LVEF at -3 years was 0.60 (AUC 0.85, sensitivity 0.74, 1—specificity 0.18). If subjects with LVEF < 0.50 at -3 years were excluded, the best cut-off was 0.615 at -3 years.

Subjects were then followed for a median 3.3 years and 48% died. Subjects with LVEF < 0.50 had significantly worse survival than those with LVEF ≥ 0.50 (p < .001); similarly, subjects with LVEF 0.50—0.59 (n = 151) had worse survival than those with LVEF ≥ 0.60 (n = 581) (p < .001). AVR improved survival across all LVEF strata. A univariate Cox proportional hazards model for all-cause mortality after diagnosis of severe AS identified age, LVEF, AVA, cardiac output, log E/e', prior MI, atrial fibrillation/flutter, haemoglobin, creatinine and moderate or moderate-severe mitral regurgitation as independent predictors.

Study two

In the second study, the authors sought to understand the prognostic value of different degrees of 'preserved LVEF' in asymptomatic or minimally symptomatic severe AS [22]. This prospective three-centre cohort study (from Amiens and Lille, France and Brussels, Belgium) included 1678 patients (mean age 76) divided into three groups, LVEF 0.50-0.54 (n = 239), 0.55-0.59 (n = 331) and ≥ 0.60 (n = 1108) and followed for a median 43.0 (IQR 22—80) months from baseline echocardiogram. Minimal symptoms included atypical chest pain and "elderly patients with minimal dyspnoea not clearly related to AS". Exclusion criteria were more than mild aortic and/or mitral regurgitation, prosthetic valves, congenital heart disease excluding bicuspid aortic valves, supra/sub-valvular AS and dynamic LVOT obstruction. Subjects operated within 3 months of the baseline echocardiogram were considered surgically managed (n = 920), the rest conservatively managed (n = 758).

Compared to the LVEF ≥ 0.60 group, where median LVEF was 0.68 (IQR 0.65—0.73), subjects with LVEF 0.50-0.54 (median 0.53) were more likely to be male, have prior atrial fibrillation or prior MI, and have larger LV end-diastolic and end-systolic diameters (LVEDD median 49 vs 46 mm, LVESD median 33 vs 27 mm, p < .001).

Five-year survival was 59 ± 4%, 74 ± 2% and 72 ± 2% in the LVEF 0.50-0.54, 0.55-0.59 and ≥ 0.60 groups respectively (log rank p < .001). Using a single LVEF cut-off, five-year survival was 59 ± 4% (LVEF 0.50-0.54) vs 72 ± 2% (LVEF ≥ 0.55) (log rank p < .001). For LVEF 0.50-0.54, survival decreased per 1% decrement in LVEF (adjusted HR 0.86, 95% CI 0.75-0.97). After adjustment for covariates (age, sex, body surface area, hypertension, CAD, history of MI, history of atrial fibrillation, comorbidity index, AVA), no significant differences in

overall mortality were found between the LVEF 0.55-0.59 and ≥ 0.60 groups, but the LVEF 0.50-0.54 group showed excess mortality when compared with subjects with LVEF ≥ 0.60 (hazard ratio (HR) 2.29, 95% CI 1.68-3.17). The same picture held irrespective of conservative or surgical management, sex, and when the reference group was all subjects with LVEF ≥ 0.55.

Study three

The third, a registry cohort study from the Heart Valve Clinic International Database using data from ten heart valve clinics across Europe, Canada and the USA, included 1375 patients with asymptomatic moderate or severe AS and LVEF ≥ 0.50 at entry and followed for a mean 27 months (range 2-224) [20]. Exclusion criteria included congenital heart valve disease, more than mild mitral, tricuspid or pulmonic valve disease, and prior valve surgery.

In subjects with severe AS at entry (n = 861, mean age 72), baseline LVEF (mean ± SD) was 0.65 ± 0.073. Taken as categorical variables, independent predictors of all-cause mortality on multivariable analysis were LVEF 0.50-0.59 (HR 5.01, 95% CI 2.93-8.57), peak aortic velocity > 5.0 m/s (HR 2.05, 95% CI 1.01-4.16), COPD (HR 2.56, 95% CI 1.19-5.48), age and systolic BP. Taken as continuous variables, independent predictors of all-cause mortality were LVEF, COPD, age and systolic BP. ROC analysis indicated that the best cut-off values for predicting overall mortality were 0.596 for LVEF (AUC 0.73, sensitivity 81%, specificity 56%) and 4.7 m/s for peak aortic velocity (AUC 0.50, sensitivity 30%, specificity 80%).

After AVR, subjects with LVEF 0.50-0.59 had lower overall survival (mean ± SD) than those with LVEF ≥ 0.60 (at 2 years 67 ± 7 vs 87 ± 5%; at 4 years 63 ± 8 vs 78 ± 4%; at 6 years 63 ± 8 vs 69 ± 7%; p = .02). Similarly, after AVR, subjects with peak aortic velocity ≥ 5 m/s had lower overall survival than those with peak velocity < 5 m/s (at 2 years 73 ± 8 vs 84 ± 2%; at 4 years 65 ± 10 vs 78 ± 4%; at 6 years 54 ± 13 vs 70 ± 6%; p = .03). An AVA < 0.8 cm^2 predicted significantly worse overall mortality.

In subjects with moderate AS at entry (n = 514, mean age 68), LVEF was 0.66 ± 0.069. ROC analysis indicated the best cut-off baseline LVEF for predicting overall mortality was 0.64.

Discussion

To summarise: three studies of subjects with asymptomatic or minimally symptomatic severe AS were reviewed. In the first, subjects with asymptomatic severe AS and LVEF < 0.50 at time zero had been experiencing a fall in LVEF from time -3 years, during which time the AS progressed from moderate to severe; in particular, LVEF deterioration preceded the development of AVA < 1.0

cm^2 and accelerated when the AVA reached 1.2 cm^2. However, subjects with LVEF ≥ 0.50 maintained mean LVEFs of 0.642 across this period. Furthermore, subjects with LVEF 0.50-0.59 had higher overall mortality than those with LVEF ≥ 0.60 and the best cut-off LVEF at -3 years to predict LVEF < 0.50 at time of diagnosis of severe AS was 0.60 [21]. In the second study, subjects with asymptomatic or minimally symptomatic severe AS and LVEF 0.50-0.54 had worse survival compared with those with LVEF ≥ 0.55, irrespective of conservative or surgical management. ROC analysis was not performed to find the best cut-off [22]. In the third study, subjects with LVEF 0.50-0.59 had higher overall mortality than those with LVEF ≥ 0.60 and the best cut-off LVEF to predict overall mortality was 0.60 [20].

Although the studies were discordant with regards to inclusion of subjects with concomitant moderate mitral regurgitation, taken together we can infer that in some ventricles with "low-normal" LV function (LVEF 0.50—0.59), even moderate AS poses enough of an afterload challenge to be associated with LVEF deterioration. These ventricles may in some way be predisposed to decompensation with lower degrees of afterload challenge than other ventricles. This supports the argument that "normal LVEF" in moderate AS be defined as "at least" 0.60 [21], and raises the prospect of prospective trials randomizing patients with moderate AS and LVEF < 0.60 to early intervention. One challenge would be that if these ventricles are intrinsically more intolerant of pressure overload, they would fare worse in the case of patient-prosthesis mismatch, and stringent efforts to avoid this would be required.

We can also question the paradigm of the natural history of LV decompensation in the face of chronic pressure overload. Classically this describes the development of concentric hypertrophy which minimizes wall stress at the expense of raising filling pressures. (Wall stress is proportional to pressure × radius / wall thickness [23].) Assuming fixed intrinsic contractility, LVs experiencing higher wall stress have lower LVEF [24]. Cavity dilation is considered a late complication, where 'late' refers to 'after the development of severe AS. However, observations that some ventricles dilate earlier, when the pressure overload is moderate, imply some intrinsic (unspecified) myocardial vulnerability in a subset of patients. Such ventricles would have a lower than expected LVEF for any given wall stress.

In severe AS, "normal LVEF" might be expected to be lower than in moderate AS owing to the increased afterload. Yet two of the studies reviewed here support an LVEF cut-off of 0.60 below which a survival disadvantage accrues, the other a cut-off of 0.55. Regarding whether to raise the threshold for intervention in asymptomatic AS: no surgical randomized clinical trials exist; a trial comparing transfemoral TAVR with active surveillance is underway (NCT03042104). Until these provide further supportive data, the question will

remain debated as any raising of the threshold would significantly increase the numbers of asymptomatic patients warranting AVR: although < 1% of all subjects with severe AS were asymptomatic with LVEF < 0.50 [18], 14% of asymptomatic or minimally symptomatic subjects with severe AS and LVEF ≥ 0.50 had LVEF 0.50-0.54 [22], and 31% of asymptomatic subjects with severe AS and LVEF ≥ 0.50 had LVEF 0.50-0.59 [20]. A reasonable interim measure could be to increase screening frequency to six-monthly in those subjects with moderate AS, AVA < 1.2 cm^2, and LVEF 0.50-0.59, as these subjects had the fastest rate of decline in LVEF [21].

These studies challenge us to reconsider what we mean by normal LVEF in the presence of moderate or severe pressure overload. To my mind there are four options: (1) The LVEF is normal if it falls within expected normal ranges for age, sex, BSA and measurement technique in the absence of valvular heart disease; (2) the LVEF is normal if today's measurement compares well with serial prior measurements in the same individual prior to the development of pressure overload; (3) the LVEF is normal if after relief of pressure overload and wall stress by AVR there is an expected increase in LVEF indicating normal contractility (i.e. no permanent injury to a pressure-intolerant myocardium); (4) the LVEF is normal if (in the asymptomatic patient and all other things fixed) it is not associated with worse mid-term survival. With the first three options, the difficulty is that we need an expected afterload (or wall stress) adjustment factor for LVEF, which is unfortunately not well established in large numbers of subjects [24]. There are also the provisos that subjects > age 70 and/or hypertension comprise the majority of subjects with severe AS yet are poorly (if at all) represented in the reference range studies available, and that (for unclear reasons) a proportion of subjects with AS remodel with more pronounced concentricity, which would be expected to flatter LVEF, while others develop LBBB or atrial fibrillation, which would be expected to depress LVEF. Fortunately, the studies reviewed here now provide us convincing data supporting the fourth option. Going forward, I expect LVEF will be incorporated into more complex risk models alongside other independent predictors of mortality in asymptomatic severe AS. Until then, we now have less reason than a year ago to be complacent about the asymptomatic subject with moderate or severe AS and an LVEF 0.50-0.59.

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