First phase ejection fraction in aortic stenosis; a useful new measure of early left ventricular systolic dysfunction

Sahrai Saeed[1], Gu Haotian[2], Ronak Rajani[3], Phil Chowienczyk[2], and John Chambers[4]

[1]Haukeland University Hospital
[2]Affiliation not available
[3]St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust
[4]St. Thomas Hospital

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Abstract

In aortic stenosis (AS), a left ventricular (LV) ejection fraction (EF) <50% or symptoms are class I indications for aortic valve intervention. However, an EF <50% may be too conservative since subendocardial fibrosis may already have developed. An earlier marker of LV systolic dysfunction is therefore needed and first phase EF (EF1) is a promising new candidate. It is the EF measured over early systole to the point of maximum transaortic blood flow. It may be low in the presence of preserved total LV EF since the heart may compensate by recruiting myosin motors in later systole. The EF1 is inversely related to the grade of AS and directly related to markers of subendocardial fibrosis like late gadolinium enhancement on cardiac magnetic resonance scanning. A reduced EF1 (<25%) predicts adverse clinical events better that total EF and global longitudinal strain. We suggest that it is worth exploring as an indication for surgery in patients with asymptomatic severe AS.

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Sahrai Saeed [1,2], Haotian Gu [3], Ronak Rajani [2], Phil Chowienczyk [3], John B. Chambers [2]

Affiliations

[1]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; [2]Cardiothoracic Centre, Guy's and St Thomas' Hospitals, London; [3]BHF Centre of Research

Excellence, King's College London, London, UK.

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Corresponding author:

Sahrai Saeed

Department of Heart Disease,

Haukeland University Hospital, Bergen, Norway

E-mail:*sahrai.saeed@helse-bergen.no*

Abstract

In aortic stenosis (AS), a left ventricular (LV) ejection fraction (EF) <50% or symptoms are class I indications for aortic valve intervention. However, an EF <50% may be too conservative since subendocardial fibrosis may already have developed. An earlier marker of LV systolic dysfunction is therefore needed and first phase EF (EF1) is a promising new candidate. It is the EF measured over early systole to the point of maximum transaortic blood flow. It may be low in the presence of preserved total LV EF since the heart may compensate by recruiting myosin motors in later systole. The EF1 is inversely related to the grade of AS and directly related to markers of subendocardial fibrosis like late gadolinium enhancement on cardiac magnetic resonance scanning. A reduced EF1 (<25%) predicts adverse clinical events better that total EF and global longitudinal strain. We suggest that it is worth exploring as an indication for surgery in patients with asymptomatic severe AS.

Keywords: Ejection fraction, First phase ejection fraction, Echocardiography, Aortic stenosis, Systolic left ventricular function, Prognosis

Introduction

Aortic stenosis (AS) is the most common type of valvular heart disease in individuals >65 years requiring valve replacement. Current class I indications for surgery are the presence of symptoms and/or left ventricular (LV) ejection fraction (EF) <50% [1-2]. However, an LV EF <50% may be too conservative since myocardial fibrosis may already be well established, and clinical outcome and LV recovery after intervention is then suboptimal [3-8]. There is therefore a need for more sensitive markers of early LV systolic dysfunction. A number of echocardiographic measures such as tissue Doppler S', midwall shortening, mitral annular plane systolic excursion, or global longitudinal strain (GLS) [9-11], or biomarkers including BNP or late gadolinium enhancement (LGE) on cardiac magnetic resonance [12-13] may detect LV systolic dysfunction earlier than LV EF and better risk stratify patients with AS [9-10].

First phase EF (EF1) has recently been described as a potentially more reliable marker of early LV systolic dysfunction in hypertension or AS. The purpose of the present focused clinical review is to summarize what is known about EF1, and suggest how it may be useful in patients with asymptomatic AS.

Pathophysiology, definition and measurement

The Frank-Starling mechanism relates end-systolic pressure to end-systolic volume. At myofibril level this involves the binding of myosin motors to actin. This is partly effected by a calcium-dependent structural change in the thin filament. However, in addition there is evidence for a thick filament-related mechano-sensing process of unlocking myosin motors in response to high stress [14-15]. This may allow the heart to compensate for impaired contraction in early systole by recruiting myosin motors to preserve total EF at the expense of a slower sustained contraction.

EF1 is the early ejection fraction to the point of maximum LV contractility which coincides approximately with the point of maximum transaortic blood velocity (Figure 1). It can be measured on transthoracic echocardiography with a methodology similar to global LV EF by Simson biplane rule (Fig. 1A-D) [16-19]. However, instead of end-systolic volume (ESV), volume at the point of peak aortic flow (SV1) on the transaortic continuous wave signal is used in the calculation (Figure 1E-G). An EF1 <25% of total EF taken as a cut-point for low [17].

Satisfactory intraobserver and interobserver coefficients of variation of $6.7 \pm 3.6\%$ and $9.8 \pm 6.1\%$, respectively have been shown [17], and intraclass correlation coefficients of 0.94 (95% CI: 0.85-0.98) for intraobserver

variability and 0.88 (95% CI: 0.67-0.95) for interobserver variability [18].

Clinical significance

EF1 is load dependent but also reflects intrinsic subendocardial fibrosis. It is inversely related to the grade of AS severity, pulse pressure/SVi ratio (an echocardiographic marker of arterial stiffness) and valvular-arterial impedance (global LV load) [18-19]. Bing et*al.* [19] found a low EF1 (<25%) in 45% patients with AS. Low EF1 was associated with high valvular-arterial impedance (Zva), high indexed extracellular volume and infarct pattern LGE independent of age, gender and serum BNP level.

In early systole, there is initial shortening of the LV subendocardial long-axis fibres and for this reason a reduced EF1 is associated with reduced long-axis function assessed by mitral annular S' velocity on tissue Doppler or GLS (Fig. 2). However, EF1 appears prognostically more useful than echocardiographic measures of long-axis function. In one study [19], GLS in patients with normal versus low EF1 was similar with a borderline statistical difference (-18.0 versus -17.7%, p=0.047), which was, however, clinically negligible.

A reduced EF1 of <25% normalized in the majority of patients (68%) following AVR [19]. This shows that afterload mismatch and potentially diffuse interstitial fibrosis may be reversible following AVR. Therefore, a low EF1 may be an early enough marker of the need for surgery to expect full LV recovery. It is also possible that EF1 may identify patients with paradoxical low flow low gradient severe AS and preserved or supranormal EF who would benefit prognostically from valve intervention [20].

Prognostic value

In a preliminary study of asymptomatic patients with moderate or severe AS, an EF1 <25% was a strong and independent predictor of events at 2 years (AVR, cardiac related hospitalizations and death) [17]. Indeed, EF1 was a stronger predictor of events than GLS irrespective of AS severity [17]. The HR for all-cause mortality at 2 years was 17.4 (95% CI 5.5 to 55.2) adjusted for mean pressure gradient, GLS, LV mass index and transaortic flow rate. Furthermore, in a receiver-operating characteristic (ROC) curve, the performance of EF1 in terms of prediction of events at 2-year follow-up was substantially better than global EF, GLS and transaortic flow rate [17]. Similarly, Bing et al. [19] also showed that low baseline EF1 was associated with a 5.6-fold increased risk of AVR or death (HR 5.6: 95% CI 3.4 to 9.4), but GLS (HR 1.54: 95% CI 0.92 to 2.6) and EF were not (HR 0.99: 95% CI 0.96 to 1.00). However, the incremental utility of EF1 in AS, as well as serial changes during echocardiographic surveillance for asymptomatic patients with AS were not explored in these retrospective studies [17,19] and should be investigated in future prospective studies.

Conclusion

EF1 is a useful marker of early LV systolic dysfunction in AS and can be accurately measured on transthoracic echocardiography. A reduced EF1 (<25%) is common in patients with AS with preserved LV EF, and predicts adverse outcomes better than conventional measures of longitudinal LV function like GLS. It may therefore become an indication for surgery in patients with asymptomatic severe AS. This now needs to be tested prospectively in randomized controlled trials.

Conflict of Interest: The authors declare that they have no conflict of interest.

Author contributions: SS and JBC contributed to the conception of the review, performed the literature search and data analysis, and drafted the manuscript. HG, RR and PC critically revised the work and approved the final manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. Measurement of EF1 in a patient with severe AS (Vmax > 4 m/s). End diastolic and systolic volumes (EDV) are measured by Simpson biplane method (A-D). Then time to peak velocity, 107 ms, is measured on the transaortic continuous wave Doppler signal (E). From the heart rate and frame rate the frame corresponding to peak aortic flow is then identified and the systolic volume (SV1) measured in biplane (F and G) giving a value 65 mL. EF1 is then calculated as 100 x (EDV-SV1)/EDV giving a value 21%. Total EF is normal at 66% but EF1 is reduced (<25%). LV, left ventricle; RV, right ventricle.

Figure 2. Reduced septal and lateral annular S' (both 4 cm/s) in a patient with severe aortic stenosis and normal global EF (66%), but reduced EF1 (21%).

Figure 3. Volume-Time curve of a patient with severe AS, normal EF=65.4%, but reduced EF1=19.7%.