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## ► To cite this version:

Hélène Martel, Arnaud Rique, Chiara Piazzai, Julien Mancini, Robinson Gravier Dumonceau, et al.. Ejection Fraction Basal Strain Ratio: A New Composite Echocardiographic Deformation Parameter Allowing Differentiation of Cardiac Amyloidosis From Hypertrophic Cardiomyopathies. *Journal of The American Society of Echocardiography*, 2023, 36 (5), pp.555-557. 10.1016/j.echo.2022.12.021 . inserm-04546375

**HAL Id: inserm-04546375**

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Submitted on 16 Apr 2024

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## **Ejection fraction basal strain ratio (EFBSR), a new composite echocardiographic deformation parameter allowing differentiation of cardiac amyloidosis from hypertrophic cardiopathies.**

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**Word count:** 763

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**Key words:** Cardiac Amyloidosis – Hypertrophic Cardiomyopathy – Longitudinal Strain – Echocardiography

Early diagnosis of cardiac amyloidosis (CA) is challenging and relies on a testing algorithm including echocardiography, bone scintigraphy, serum free light-chain ratio and sometimes cardiac magnetic resonance imaging and endomyocardial biopsy <sup>1</sup>. Because CA is known to be characterized by a more severe decline in longitudinal deformation parameters as compared with radial function parameters (left ventricular ejection fraction [LVEF]), echo strain ratio parameters have been proposed to differentiate CA from other causes of **increased wall thickness**, including RELAPS (ratio between average apical strain and the sum of average mid and basal strain) and EFSR (ratio between LVEF and global longitudinal strain (GLS)). However, their respective value is debated <sup>2,3,4</sup>. Since longitudinal dysfunction usually predominates in basal segments (apical sparing), we postulated that a new parameter focusing on both LVEF and *basal* LV deformation: EFBSR (Ejection Fraction Basal Strain Ratio) will better discriminate patients with CA **from LV hypertrophic cardiopathies** than echo or strain usual parameters and ratios.

The main objective of this study was to compare EFBSR with other echo and strain other parameters in a population of 89 patients with CA and 209 patients with another cause of **increased wall thickness**. All patients were asked to participate in this research protocol and provided informed consent.

Echocardiographic studies were performed **in standard devices** (GE, Vivid 9). **Two dimensional longitudinal strain was measured using** EchoPAC<sup>TM</sup> software (**GE Healthcare**). All patients underwent comprehensive two-dimensional echocardiography including conventional echocardiographic parameters: LVEF (by biplane Simpson method), mean Inter-Ventricular Septum wall thickness at end-diastole (IVSd), LV volumes and diameters, LV Global Longitudinal Strain (GLS, %), Left atrial volume index (LAVi) and cardiac index (CI) as recommended <sup>5,6</sup>. Strain-derived ratios were calculated offline: RELAPS <sup>2</sup>, EFSR <sup>4</sup> and EFBSR, our new parameter (ratio between LVEF and basal longitudinal strain (calculated as the average of the longitudinal strain of the six basal segments)). All analyses were performed using R 4.0 software and the packages *pROC* and *MatchIt*.

We included 298 subjects in La Timone hospital (Marseille, France) from January 2018 to December 2020, of which:

- 89 patients with CA (77 ± 11 years, 72% male, LVEF: 56.2 ± 12.8%, IVSd: 18 ± 4 mm, and GLS: -10.5 ± 3.4%),
- 137 patients with hypertrophic cardiomyopathies (HCM) (50 ± 17 years, 73% male, LVEF: 69.1 ± 9.7%, IVSd: 19 ± 6 mm, and GLS: -14.6 ± 4.1%),

- 52 patients with severe aortic stenosis (AS) with myocardial remodeling ( $80 \pm 9$  years, 63% male, LVEF:  $58.8 \pm 15.0\%$ , IVSd:  $14 \pm 3$  mm, and GLS:  $-13.8 \pm 4.6\%$ ),
- 20 patients with LV hypertrophy due to systemic arterial hypertension (SH) ( $64 \pm 17$  years, 60% male, LVEF:  $71.4 \pm 5.7\%$ , IVSd:  $13 \pm 1$  mm, and GLS:  $-19.0 \pm 2.7\%$ ).

GLS, mid and basal strains, and the three strain-derived ratios were significantly different **between CA group and the combined group of LV hypertrophies** ( $p < 0.01$ ) (table 1).

Concerning the subgroup analysis for the ratio, the results were as follows (p-values concern comparisons between each hypertrophic pathology to CA using t-tests with Bonferroni adjustment for multiple comparisons after checking global significant difference in ANOVA [all  $p < 0.01$ ]):

- EFBSR: CA ( $14.8 \pm 12.2$ ), HCM ( $5.9 \pm 2.3$ ,  $p < 0.01$ ), AS ( $5.4 \pm 2.0$ ,  $p < 0.01$ ), SH ( $4.9 \pm 0.9$ ,  $p < 0.01$ )
- RELAPS: CA ( $2.5 \pm 1.2$ ), HCM ( $1.3 \pm 0.4$ ,  $p < 0.01$ ), AS ( $1.3 \pm 0.4$ ,  $p < 0.01$ ), SH ( $1.5 \pm 0.3$ ,  $p = 0.02$ )
- EFSR: CA ( $5.8 \pm 1.8$ ), HCM ( $5.2 \pm 2.6$ ,  $p = 0.20$ ), AS ( $4.6 \pm 1.6$ ,  $p < 0.01$ ), SH ( $3.8 \pm 0.4$ ,  $p < 0.01$ )

The comparison of the accuracy of the following parameters (LVEF, GLS, RELAPS, EFSR and EFBSR) to discriminate CA from other causes of LV **increased wall thickness** using ROC curves (Figure 1) showed that EFBSR and RELAPS presented the best performance (Area Under the Curve (AUC): 0.89; 95% CI: 0.84-0.94 and AUC: 0.91; 95% CI: 0.87-0.94 respectively). Among all the parameters, when Youden index was used to select cutoffs maximizing sensitivity and specificity with equal weight, EFBSR had the best specificity (90.0%, versus 82.3% for RELAPS), whereas RELAPS had the best sensitivity (83.1% vs 78.7% for EFBSR). EFBSR ranged from 35.25 to 1.83 and the cutoff value to differentiate **CA from hypertrophic cardiopathies** was an EFBSR  $> 7.75$ .

An additional analysis performed among 68 patients with CA matched according to their LVEF and IVSd (using optimal pair matching method) to 68 patients from the combined group of LV hypertrophies, confirmed that EFBSR and RELAPS presented the best performance (AUC: 0.91; 95% CI: 0.85-0.96 and AUC: 0.91; 95% CI: 0.87-0.96 respectively).

**As a second limitation, the researchers did not measure LVEF and longitudinal strain blinded to the diagnosis, but several clinicians performed the echocardiographies and ratios were calculated later by another operator.**

**Our study demonstrates that, EFBSR, can accurately differentiate CA from other causes of increased wall thickness and may be of value when the RELAPS cannot be calculated due to difficulty with measuring the apical strain.**

**Disclosure:**

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (HM, AR, CP, JM, FA, AD, AG, ACC, SR, SH) ((2) drafting the article or revising it critically for important intellectual content (HM, AR, CP, KNG, GH), (3) final approval of the version to be submitted (all). HM and GH are responsible for the overall content as guarantor(s).

**There are no competing interests for any authors.**

**There are no funders to report for this submission**

**Financial disclosure:** none

### **Tables and figures legend**

Table 1. Comparison of echocardiographic parameters between CA group (n=89) and other causes of LV hypertrophy group (HCM, AS and SH patients).

Figure 1: ROC curves of LVEF, GLS, RELAPS (RAS), EFSR and EFBSR to discriminate CA from another cause of LV hypertrophy.

**Table 1: Comparison of echocardiographic parameters between CA group (n=89) and other causes of LV hypertrophy group (HCM, AS and SH patient)**

	CA group (n=89)	HCM + AS + SH group (n=209)	<i>p-value</i>	AUC
Age, yrs	74.5±10.6	57.3±20	<0.01	
Sex (Male), n (%)	72 (80.9)	144 (68.9)	0.03	
IVSd, mm	18.3 ± 3.5	17 ± 5.7	0.02	0.64
PWTd, mm	15.1 ± 3.5	11.7 ± 2.9	<0.01	0.78
LVMi, g/m <sup>2</sup>	187.8 ± 54.3	149.3 ± 51.5	<0.01	0.71
LVEDd, mm	45 ± 7.2	45.4 ± 7.2	0.66	
LVESVi, mL/m <sup>2</sup>	26.8 ± 14.6	19.5 ± 15.9	0.01	0.69
LVEDVi, mL/m <sup>2</sup>	61.4 ± 22.3	55.8 ± 28.3	0.12	
LAVi, mL/m <sup>2</sup>	52.1 ± 18.3	41.7 ± 23.8	<0.01	0.67
LVEF, %	56.2 ± 12.8	66.1 ± 11.8	<0.01	0.73
CI, L/min/m <sup>2</sup>	2.4 ± 1.0	4.9 ± 3.1	<0.01	0.83
GLS, %	-10.5 ± 3.4	-14.8 ± 4.4	<0.01	0.78
Basal strain, %	-5.5 ± 3.1	-12.7 ± 3.6	<0.01	0.93
Mid strain, %	-9.4 ± 3.4	-14.1 ± 4.4	<0.01	0.80
Apical strain, %	-16.5 ± 4.9	-17.7 ± 6.7	0.08	
EFBSR	14.8 ± 32.3	5.7 ± 2.2	<0.01	0.89
RELAPS	2.5 ± 1.2	1.3 ± 0.4	<0.01	0.91
EFSR	5.8 ± 1.8	4.9 ± 2.3	<0.01	0.71

Values are given as n (%) or mean ± standard deviation and compared using  $\chi^2$  or t-tests respectively.

AUC: Area Under the ROC Curve for every echo derived parameter significantly different between the two groups, HCM: Hypertrophic cardiomyopathies, AS: Aortic Stenosis, SH: Systemic hypertension, IVSd: Inter Ventricular Septum wall thickness at end-diastole, PWTd: Posterior Wall Thickness at end-diastole, LVMi: Left Ventricular Mass index, LVEDd: Left Ventricular end-diastole Diameter, LVESVi/LVEDVi: Left Ventricular Systolic/Diastolic Volume index, LAVi: Left Atrial Volume index, LVEF: Left

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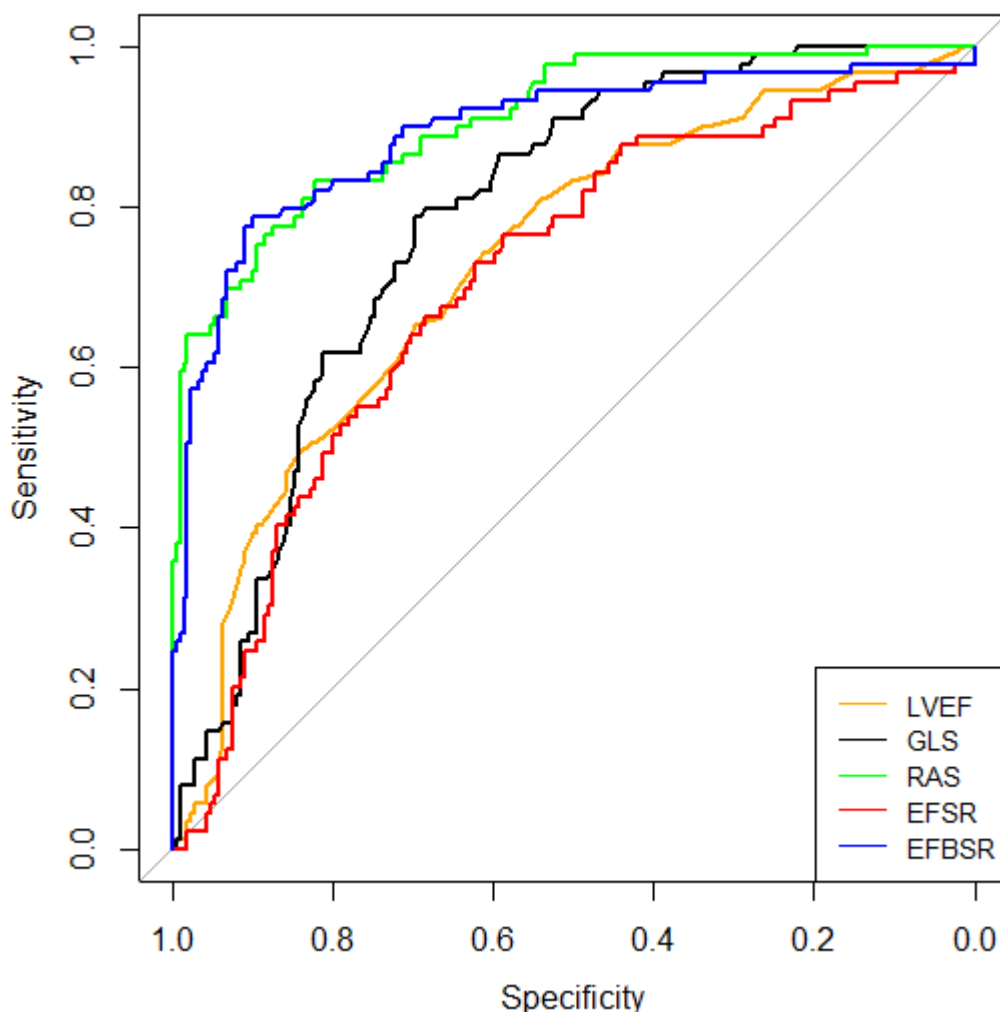
Ventricular Ejection Fraction, CI: Cardiac Index, GLS: Global Longitudinal Strain, EFBSR: Ejection Fraction Basal Strain Ratio ( $EFBSR = EF/\text{Basal longitudinal strain}$ ), RELAPS: RELative APical Sparring, and EFSR: Ejection Fraction Strain Ratio ( $EFSR = EF/GLS$ ).

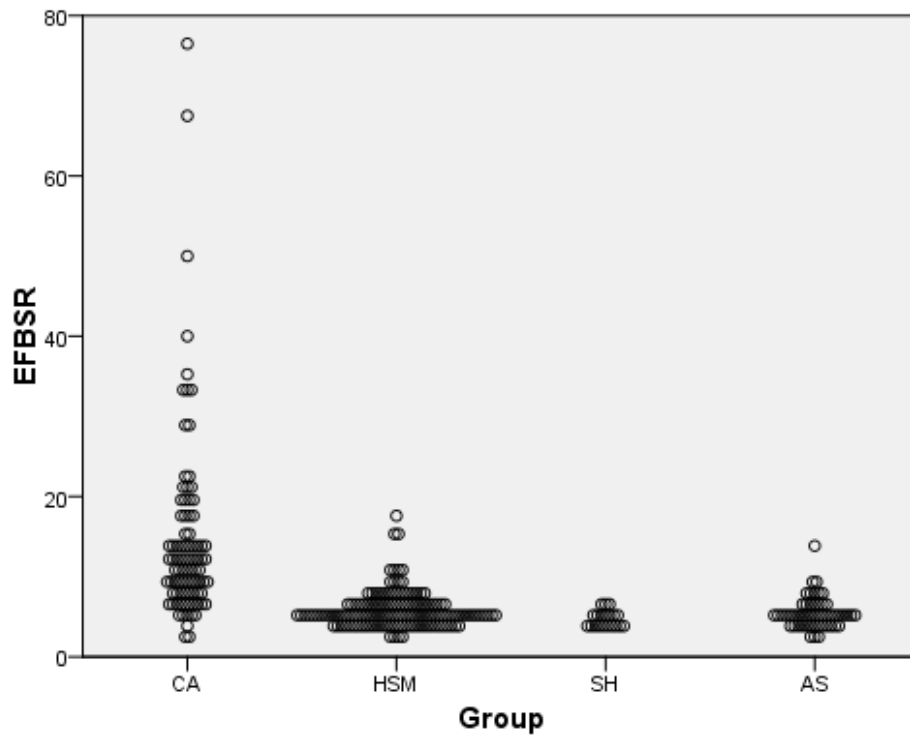


**Figure 1: ROC curves of LVEF, GLS, RELAPS (RAS), EFSR and EFBSR to discriminate CA from another cause of LV hypertrophy.**

ROC curves characteristics (AUC: Area Under the Curve; 95%CI: Confidence Interval; cut-off point (defined as maximizing Youden index); Se (%): sensitivity; Sp (%): specificity, p-value: paired comparison with AUC of EFBSR using Delong test):

Left ventricular ejection fraction or LVEF (AUC: 0.73; 95%CI 0.67-0.79 cut-off: 65.2; Se: 74.2%; Sp: 61.2%,  $p < 0.01$ ); Global longitudinal strain or GLS (AUC: 0.78; 95%CI 0.73-0.84; cut-off: 12.74; Se: 78.7%; Sp: 69.9%,  $p < 0.01$ ); Relative apical sparing or RAS (AUC: 0.91; 95%CI 0.87-0.94; cut-off: 1.68; Se: 82.3%; Sp: 83.1%,  $p = 0.40$ ); Ejection fraction strain ratio or EFSR (AUC: 0.71; 95%CI 0.64-0.77; cut-off: 4.46; Se: 76.4%; Sp: 58.9%,  $p < 0.01$ ); Ejection fraction basal strain ratio or EFBSR (AUC: 0.89; 95%CI 0.84-0.94; cut-off: 7.75; Se: 78.7%; Sp: 90.0%).





**Abbreviations**

AS: Aortic Stenosis

CA: Cardiac Amyloidosis

EFSR: Ejection Fraction Strain Ratio

EFBSR: Ejection Fraction Basal Strain Ratio

GLS: Global Longitudinal Strain

SH: Systemic Arterial Hypertension

HCM: Hypertrophic Cardiomyopathy

LVEF: Left Ventricular Ejection Fraction

RELAPS or RAS: Relative Apical Sparring

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