SCIENTIFIC RESEARCH

MYOCARDIAL STRAIN TO PREDICT MID-TERM MORTALITY AND RE-HOSPITALIZATION IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

Nguyen Thi Thu Hoai,**, Pham Tuan Viet*, Tran Ngoc Lan*, Ngo Thi Huong*, Luu Bich Dao*, Hoang Thi Hoa****

SUMMARY

Background: Heart failure (HF) is a severe clinical syndrome caused by diverse etiologies. Classically left ventricle ejection fraction (LVEF) has been used as a diagnostic marker as well as to subdivide HF into 3 groups (HFpEF, HFmEF and HFrEF). However, the prognostic value of this index is not consistent in comparison to LV strain (GLS, GCS) which are not only able to detect heart failure at a very early stage (precede to EF change) but also to predict the primary outcome including HF readmission and death. The prognostic role of LV strain is independent and incremental to conventional echocardiographic parameters.

Methods: 67 patients diagnosed with chronic HFrEF (EF < 40%) at Vietnam National Heart Institute were consecutively enrolled in our study from January 2016 to September 2016. Clinical data were comprehensively evaluated and conventional echocardiographic parameters and two LV strain indices (GLS & GCS) were measured using speckle-tracking. All patients were followed up for all-cause 12-month readmission or death after discharge. The relation between echocardiographic parameters and clinical events was analyzed in Cox proportional hazard model.

Results: GLS had a prognostic value of composite events after being adjusted with age, sex, heart rate, SBP, DBP, NT-ProBNP, renal clearance, LVEF and LVDd. GLS (cut-off = -7.5%; AUC = 0.738; p = 0.003) was a stronger predictor of composite event compared to LVEF (AUC= 0.66, p = 0.042) LVDd (AUC = 0.637; p = 0.025), LA diameter (AUC = 0.614, p = 0.03), NT-ProBNP (AUC = 0.663; p = 0.04) and hs-Troponin T (AUC = 0.592; p = 0.039).

Conclusion: Global longitudinal strain is and strong and independent predictor of readmission and death in patients with heart failure with reduced ejection fraction.

Keywords: *heart failure, left ventricular function, global longitudinal strain, ejection fraction.*

** Vietnam National Heart Institute, Bach Mai Hospital*

*** Department of Internal Medicine, University of Medicine and Pharmacy, Hanoi National University*

**** Hanoi Medical University*

I. INTRODUCTION

Heart failure (HF) is a severe complication originating from multiple cardiovascular and predicts the primary outcome of HF patients, particularly HFrEF group [1]. In a wide range of HF complications, mid-term all-cause death and readmission attract great attention. Although LVEF and laboratory indices including NT-ProBNP, and hs-Troponin T have been used for decades to stratify HF patients, these conventional parameters have their limitations [1], [2]. A novel parameter like LV strain which can predict all-cause mortality and readmission during 12 months after discharge is desired [3], [4], [5], [6]. Thus, this study is aimed to evaluate the association between two LV strain parameters (GLS and GCS) with HF composite events (death and readmission) in patients diagnosed with chronic HFrEF.

II. METHODS

Study subjects: A total of 67 patients diagnosed with chronic HFrEF (LVEF<40%) at Vietnam National Heart Institute were consecutively enrolled in the study from January 2016 to September 2016 according to ESC/ESH guidelines[2]. The exclusion criteria were: Acute coronary syndrome, severe comorbidities, atrial fibrillation or high-grade atrioventricular block, patients rejected to participate in the study, and patients had suboptimal echocardiographic images.

Clinical data: Clinical parameters including age, sex, medical history, NYHA and basic blood test result at admission were comprehensively assessed and recorded.

Echocardiography: All patients underwent standard 2D transthoracic echocardiography (2DTTE) using only one ultrasound machine (Vivid E9, GE) integrated with dedicated speckle-tracking analysis software (ECHOPAC). Echocardiographic images were obtained and recorded in DICOM format for offline analysis. Conventional echocardiographic parameters were measured according to the guidelines of the American Society of Echocardiography (ASE) [7]. Left ventricular ejection fraction (LVEF) was measured in apical four-chamber and two-chamber views using Biplane disk assumption method. Diastolic transmitral flow velocities (E, A) were acquired in apical four-chamber view using pulsed-wave doppler. Diastolic mitral annular velocities (e', a') were also measured in the same view using tissue doppler imaging (TDI) with the sample volume placed at septal and lateral annuli to calculate average e'. Inferior vena cave diameter and respirator collapse were measured to estimate right atrium pressure (RAP) [7].

Strain Imaging: Two LV strain parameters (global longitudinal strain -GLS and global circumferential strain- GCS) were measured using the standard technic of speckle tracking echocardiography (ECHOPAC, GE). GLS was measured as the average peak values of 17 segmental longitudinal strains in three apical views (four-chamber, three-chamber, and two-chamber). The peak values of 6 segmental circumferential strains were obtained and averaged in short-axis views at the papillary muscle level to calculate GCS. LV strain parameters were automatically calculated on dedicated software (ECHOPAC) after the LV endocardial border was manually traced. The frame rate was from 60 to 100 fps.

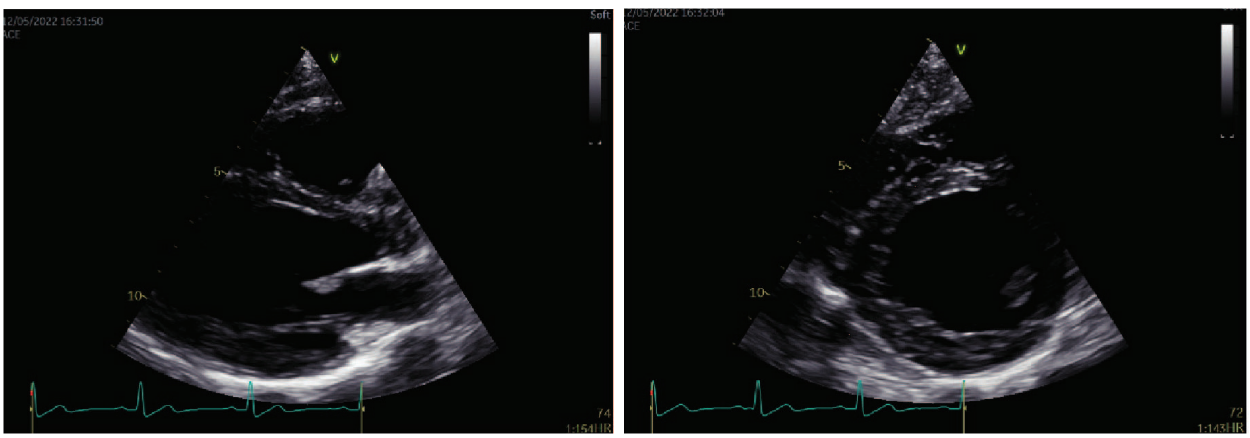

Figure 1. *Parasternal long axis view and short axis view and strain imaging measurements*

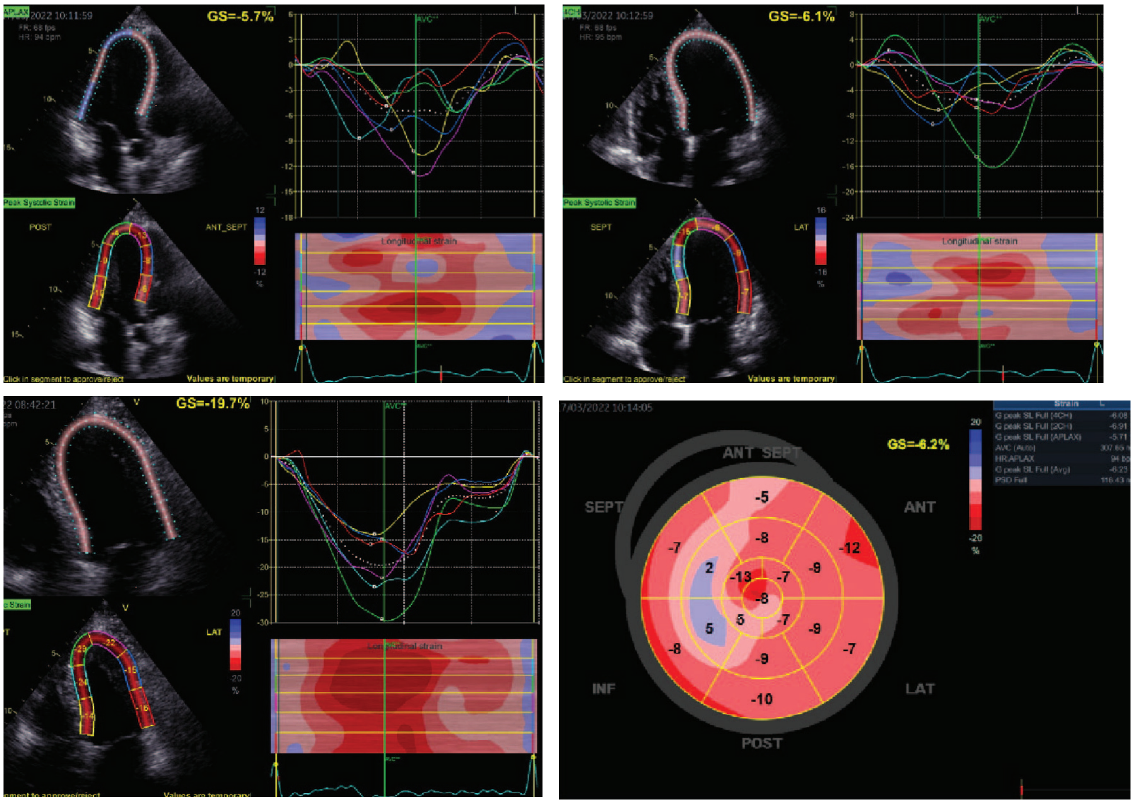

Figure 1. (Next) *Parasternal long axis view and short axis view and strain imaging measurements*

Statistical analysis: Quantitative data are expressed as mean ± SD. In case of normal distribution, the Student T-test and ANOVA test were used to assess the significance of differences between two groups and more than three groups respectively. The correlation between two quantitative variables with normal distribution was tested by Spearman linear regression index. For categorical and binomial variables, the data are expressed as a percentage (%), and $\chi 2$ or Fisher-exact test was used as appropriate. ROC was used to evaluate the value of the diagnostic investigation. If the AUC is significant, the cut-off value was identified by the J value [J = max (Sensitivity + Specitivity – 1)]. Kaplan-Meier and univariate and multivariate COX proportional hazards models were used to figure out the contribution of 12-month death or readmission. In all statistical tests, p-value below 0.05 is considered significant.

III. RESULTS

Patient characteristics: Among 67 patients enrolled in the study, the elderly group (age >60) accounts for 58.2%. The mean age was 61.73 ± 12.0 and the youngest patient diagnosed with HFrEF in our study was at age of 28. Men accounted for 83,6%. Regarding HF etiologies and risk factors, the proportion of dilated cardiomyopathy, coronary artery disease, hypertension, and diabetes mellitus were 31.3%, 23.9%; 29.8% and 14.9% respectively. In terms of HF symptoms, all patients had functional limitations from NYHA II. In particular, more than half of patients (50.1%) were classified in NYHA III.

Table 1. *Patients' characteristics*

Parameters	X ±SD or %(n)
Age (year)	61.73 ± 12.0
Heart rate (beat per minute)	92.1 ± 11.37
SBP (mmHg)	117.24 ± 18.0
DBP (mmHg)	71.79 ± 13.6
Renal clearance (L/m/1.73m^2)	67.57 ± 22
NT- proBNP (ng/mL)	1176 ± 683

hs-TroponinT (ng/mL)		0.019 ± 0.024
Hb (g/l)		129 ± 17.6
Age group	≤ 40 (%, n)	6.0 (4)
	40 – 60 (%, n)	35.8 (24)
	≥ 60 (n,%)	58.2 (39)
Sex	Men (%, n)	83.6 (56)
	Women (%, n)	16.4 (11)
Cardiac history	Hypertension (%, n)	29.86 (20)
	CAD (%, n)	23.90 (16)
	DCM (%, n)	31.34 (21)
	DM (%, n)	14.90 (10)
NYHA	NYHA II (%, n)	12.0 (8)
	NYHA III (%, n)	50.7 (34)
	NYHA IV (%, n)	37.3 (25)

(CAD: coronary artery disease, DCM: dilated cardiomyopathy, DM: diabetes mellitus, SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin

Table 2. *Echocardiographic parameters*

Echocardiographic parameters (n = 67)	Mean ± SD	Maximum	Minimum
LVDd (mm)	54.46 ± 10.5	75	40
LVEF (Biplane) (%)	31.09 ± 7.7	40	15
LA diameter (mm)	39.38 ± 13.2	52.12	23.0
E/e'(cm/s)	13.7 ± 13.2	22.8	8.6
GLS (%)	-7.3 ± 3.9	0.0	-13.0
GCS (%)	-9.1± 5.2	0.0	-16.0

(LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LA: left atrial, GLS: global longitudinal strain, GCS: global circumferential strain)

All patients in our study had a severe reduction in both GLS and GCS. The maximum GLS and GCS were -13.0% and -16.0% respectively. 45 events were occurring within 12 months after discharge, including 9 deaths and 36 readmissions (table 3). Heart rate, serum hs-Troponin, LVDd, LA diameter were significantly higher whereas systolic blood pressure, renal clearance and LVEF were significantly lower in event group (table 4). In patients with composite events, baseline longitudinal and circumferential left ventricular myocardial strain were significantly lower (GLS and GCS were less negative) (table 4).

Table 3. *Events in 12 months after discharge*

Event	n	%
Death	9	13.4
Readmission	36	53,7
Composite event	45	67.2

Table 4. *Comparison strain characteristics between 2 groups (with and without events).*

Parameters	Event group (n=45) X ± SD	No-event group (n=22) X ± SD	p
GLS	-5.21 ± 3.8	-8.6 ± 3.9	< 0.05
GCS	-7.21 ± 3.5	-13.27 ± 6.6	< 0.05

GLS (AUC = 0.738, p = 0.003) but not GCS (AUC = 0.526, p = 0.06) had prognostic value in 12-month death or readmission. The cumulative survival rate (free of events) at 12-month follow-up was 80% in patients whose GLS was more negative than -7.5% ($\chi 2$= 9.7, p =0.0043). GLS less negative than -7.5% associated with 3.75 higher risk of composite events (death and readmission) in univariate COX proportional hazards model (p = 0.003). In multivariate COX regression analysis, GLS still had a prognostic value of composite events after being adjusted with age, sex, heart rate, SBP, DBP, NT-ProBNP, renal clearance, LVEF and LVDd (table 5). GLS (cut-off = -7.5%; AUC = 0.738; p = 0.003) was a stronger predictor of composite event compared to LVEF (AUC= 0.66, p = 0.042) LVDd (AUC = 0.637; p = 0.025), LA diameter (AUC = 0.614, p = 0.03), NT-ProBNP (AUC = 0.663; p = 0.04) and hs-Troponin T (AUC = 0.592; p = 0.039).

Table 5. *Values of GLS, other echocardiographic parameters, and NT-proBNP in the prediction of events*

Variable	AUC	Sensitivity (%)	Specificity (%)	p
GLS (%)	0.738	67.3	76.7	0.003
Lad (mm)	0.614	61.9	62.7	0.027
NT-proBNP (ng/ml)	0.592	60.9	61.5	0.039
EF (%)	0.65	63.7	66.0	0.042
Dd (mm)	0.637	57.5	69.5	0.025
hs-TroponinT (ng/ml)	0.65	57.2	61.2	0.047

IV. DISCUSSION

Heart failure is a clinical syndrome with typical symptoms and signs caused by structural and functional cardiac abnormalities. LVEF is one of the most widely used parameters for the assessment of cardiac function and is a predictor of adverse events; however, the relationship between LVEF and outcomes in patients with HF is inconsistent. Among various clinical, laboratory, and echocardiographic parameters, LV myocardial strain, in particular, GLS provides an independent and incremental prognostic value of 12-month readmission and death[8] [9]. Indeed, the composite event (mortality and readmission) of HFrEF patients is a multifactorial problem that needs to be assessed comprehensively. The ideal predictor of 12-month all-cause death and readmission of HFrEF has not been established. In our study, GLS at the cut-off -7.5% showed a remarkable relationship with the primary outcome. Although LVEF has been used for many years to diagnose, classify and prognosis HF patients, this index has several limitations. LVEF measured by 2D-TTE is mostly based on the mathematical assumption which could be affected by LV geometry. Strain, in contrast, measures the myocardium directly. In patients who have advanced HF, the LV chamber becomes more spheric and the LV function may be overestimated or underestimated by 2D-LVEF. LVEF represents the percentage change of left ventricular (LV) chamber size, but not myocardial contractility. In the MUSTT study, patients with severe HF (LVEF < 30%), the LVEF showed a very low predictive value of all-cause mortality. GLS is a marker of early change of LV mechanic function. GLS has been proven as an objective parameter to assess LV mechanics and to predict cardiac mortality independently in HF patients. In other studies in patients with HF, GLS has a greater prognostic value than LVEF [9], [10], [11]. Therefore, the authors suggest that GLS should be considered the standard measurement in all patients with HF.

V. CONCLUSION

Left ventricular global longitudinal strain at the cut-off of -7.5% is a strong predictor of 12-month all-cause mortality and readmission in HFrEF patients. This prognostic value is independent and incremental to clinical, laboratory variables, and even conventional echocardiographic parameters.

REFERENCES

1. Murphy, N.F., et al., National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland. Heart, 2004. 90(10): p. 1129-36.

2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC [Published correction appears in Eur Heart J 2016;39:860]. Eur J Heart Fail 2016;18:891–975.

3. Curtis JP, Sokol SI, Wang Y, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 2003;42:736–42.

4. Mondillo, S., et al., Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med, 2011. 30(1): p. 71-83.

5. Yingchoncharoen, T., et al., Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr, 2013. 26(2): p. 185-91.

6. Saito, M., et al., Association of left ventricular strain with 30-day mortality and readmission in patients with heart failure. J Am Soc Echocardiogr, 2015. 28(6): p. 652-66.

7. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

8. Laurens F. Tops, Victoria Delgado, Nina Ajmone Marsan, and Jeroen J. Bax. Myocardial strain to detect subtle left ventricular systolic dysfunction. European Journal of Heart Failure (2017)19, 307–313

9. Eek, C., et al., Strain echocardiography predicts acute coronary occlusion in patients with non-ST-segment elevation acute coronary syndrome. Eur J Echocardiogr, 2010. 11(6): p. 501-8.

10. Rev Port Cardiol. Rangel I1, G.A., de Sousa C3, Almeida PB3, Rodrigues J2, Macedo F3, Silva Cardoso J3, Maciel MJ4., Global longitudinal strain as a potential prognostic marker in patients with chronic heart failure and systolic dysfunction. 2014: p. 33(7-8):403-9. doi: 10.1016/j.repc.2014.01.023.

11. Cho GY, Marwick TH, Kim HS, Kim MK, Hong KS, Oh DJ. Global 2-dimensional strain as a new prognosticator in patients with heart failure. J Am Coll Cardiol 2009;54:618–24.

Correspondent: Nguyen Thi Thu Hoai. Email: hoainguyen1973@gmail.com
Recieved: 18/12/2022. Assessed: 18/12/2022. Reviewed: 20/12/2022. Accepted: 21/12/2022