

## Value of longitudinal indices of the left ventricle in prediction of elevated left ventricular filling pressure in patients with preserved ejection fraction

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**Abstract: Objectives:** The principal objective of this study is to evaluate the diastolic function by Speckle Tracking Echocardiography (STE) and conventional echocardiographic indicators of diastolic dysfunction to predict invasively measured LVEDP in a patient population with preserved EF (50%). **Patients and methods:** This study (prospective) included finally 21 patients with preserved EF who underwent elective cardiac catheterization for the diagnosis of coronary artery disease or re-evaluation after coronary intervention. at BAB EL-SHE'RIYA Hospital – Al-Azhar University – Cairo – Egypt, from January, 2016 to December, 2016. At the beginning of the study 30 patients meeting both the inclusion and the exclusion criteria were enrolled then 9 patients were excluded from the study for various causes (3 patients more than mild valve lesion, 3 patients impaired systolic function, 2 had bad echo views and 1 patient had paroxysmal A Fib). **Results:** LVEDP was measured before coronary angiography was performed in 21 patients with preserved EF ( $\geq 50\%$ ) referred to elective cardiac catheterization; besides, patients enrolled underwent comprehensive echocardiographic examination before the procedure. In addition to conventional echocardiographic parameters used to evaluate diastolic function LV longitudinal strain and SR, measurements were performed using STE. E/SRIVR significantly correlated with LVEDP. When age-adjusted stepwise linear regression analysis was performed, E/SRIVR values (P 0.017) was independently correlated with LVEDP. **Conclusion:** When compared with conventional echocardiographic parameters, other longitudinal strain, and SR indices, we suggest that E/SRIVRT is a valuable parameter to evaluate diastolic function in patients with preserved EF.

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**Keywords:** Value; longitudinal indice; left ventricle; prediction; elevated left ventricular; filling; pressure; patient; preserved ejection fraction

### 1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a prevalent and growing public health problem associated with significant morbidity and mortality. HFpEF currently accounts for  $\geq 50\%$  of the general heart failure population (Yancy CW, et al., 2013). Impairment in left ventricular (LV) diastolic function has been proposed as a key pathophysiologic mediator (Lam CS, et al., 2011; Paulus WJ, et al., 2007). To be able to diagnose diastolic dysfunction, non-invasive estimation of LV filling pressures is a clinical requisite (Caruana L et al., 2000). The estimation of LV lling pressures in patients with normal ejection fraction (EF) is more challenging than in those with depressed EF. LV filling index E/E' with its wide borderline values has also some limitations in the diagnosis of diastolic function particularly when left atrial (LA) pressure is low (Previtalli M et al., 2012; Kasner M et al., 2007; Nagueh SF et al., 2009; Galderisi M et al., 2013). This involves clinical circumstances like young patients with borderline symptoms and risk factors for diastolic dysfunction. Recently, several investigations have highlighted the key role of the longitudinal diastolic function of the

LV in the pathophysiology of HFpEF, also suggesting that in patients with diastolic dysfunction the myocardial systolic function of the LV is not preserved. Myocardial strain and strain rate (SR) were recently introduced as echocardiographic parameters for quantification of diastolic function. LV diastolic SR signals can be recorded during early filling (SRE), late diastole (SRA), and isovolumetric relaxation (SRIVR). The ratio of early mitral flow (E) to SRIVR predicted LV filling pres- sure in patients in whom the E/e' ratio was inconclusive and was more accurate than the E/e' ratio in patients with normal EF and those with regional dysfunction (Wang J et al., 2007). Additionally, peak LA longitudinal strain (PALS, peak atrial longitudinal strain) during LV systole was also presented as a new index of diastolic function (Wakami K et al., 2009).

The evaluation of diastolic function by deformation imaging is promising, but needs more study of its incremental clinical value. Therefore, longitudinal deformational parameters of LV and LA, detected by speckle tracking echocardiography (STE), and conventional echocardiographic indicators of diastolic dysfunction were compared in our study to

predict invasively measured LVEDP in a patient population with preserved EF (50%).

## 2. Materials and methods

This study (prospective) included finally 21 patients with preserved EF who underwent elective cardiac catheterization for the diagnosis of coronary artery disease or re-evaluation after coronary intervention. at BAB EL-SHE'RIYA Hospital – Al-Azhar University – Cairo – Egypt, from January, 2016 to December, 2016.

At the beginning of the study 30 patients meeting both the inclusion and the exclusion criteria were enrolled then 9 patients were excluded from the study for various causes (3 patients more than mild valve lesion, 3 patients impaired systolic function, 2 had bad echo views and 1 patient had paroxysmal A Fib).

### Inclusion criteria:

1. Participant agreement,
2. Sinus rhythm,
3. None or mild aortic and mitral regurgitation or stenosis,
4. None Prosthetic mitral valve,
5. Preserved LV systolic dysfunction (EF  $\geq$ 50%),
6. Preserved renal function.

### Exclusion criteria:

- 1- Refusal of the patient to participate in the study,
- 2- Non-sinus rhythm,
- 3- More than mild aortic and mitral regurgitation or stenosis,
- 4- Prosthetic mitral valve,
- 5- LV systolic dysfunction (EF, 50%),
- 6- Acute coronary syndrome,
- 7- Renal failure.

**All the patients had been subjected to the following:**

**1- Acquisition of written consent of agreement of participation.**

**2- Personal data collection, demographic and risk factors assay** such as age, gender, presence or absence of hypertension, diabetes, smoking, dyslipidemia and family history of IHD.

**3- Conventional echocardiographic examination**

All echocardiographic examinations were performed before the patient was admitted to cardiac catheterization laboratory, using a commercially available system (iE 33, Philips, Bothel, USA) equipped with an S5-1 probe and recorded for offline analysis (Xcelera Workstation and QLAB; Advanced Quantification Software V.8.1, Philips). Individuals were instructed to hold their breath, and images were coupled with electrocardiographic recordings. Measurements were done offline later by a single

investigator who was blinded to the clinical and catheterization data.

M-mode measurements were performed according to the criteria of the European Association of Cardiovascular Imaging. Three consecutive cycles were averaged for every parameter. LA dimension and LV end- systolic (LVESD) and end-diastolic diameters (LVEDD) were measured. LV ejection fraction was estimated by biplane Simpson's rule.

Early (E) and late (A) wave velocities, E/A ratio were measured from the mitral inflow profile. Isovolumetric relaxation time (IVRT) was also measured using pulsed-wave Doppler using previously validated and recommended methods (Yancy CW et al. 2013). To acquire tissue Doppler imaging data, the Nyquist limit was set at 15–20 cm/s, and minimal optimal gain was used. The myocardial systolic (S'), early diastolic (E'), and late diastolic (A') velocities were obtained at the septal and lateral mitral annulus by placing a sample volume (Nagueh et al., 2009).

### 4- Speckle tracking imaging

For speckle tracking analysis, three cycles were recorded at a frame rate of  $\geq$ 45 fps, and were averaged for strain analysis. Aortic valve opening and closing times were measured from the LV outflow Doppler profile and were incorporated in the speckle tracking strain profile in order to exclude post-systolic components. From three manually selected land-mark points (lateral and septal mitral annulus and LV apex) in apical views, LV endocardial borders were automatically detected by the software. Subsequently, automatic tracking of myocardial speckles was performed throughout the whole cardiac cycle. Manual corrections of the border tracings were avoided as far as possible. Global longitudinal strain (GLS) and SR curves were obtained for apical four-chamber, three-chamber, and two-chamber views; subsequently, the software (Q LAB V8.1 application for two-dimensional strain analysis) provided LV model consisting of all segments. Systolic GLS was obtained by averaging peak longitudinal strain of 17 segments. Similarly, SRIVR was determined, E/SRIVR was also calculated (Suzan Hatipoglu et al. 2015).

### 5- Cardiac catheterization

Cardiac catheterization was performed after the echocardiographic image acquisition was completed. During catheterization, heart rate and blood pressure were continuously monitored. In all patients, a fluid-filled 6-F pigtail catheter was inserted percutaneously from the right femoral artery and advanced to the LV. Before the contrast agent was injected into the coronary arteries, the LV pressure was obtained. After 10 consecutive beats were recorded, the measurement of LVEDP was made at the peak of R-wave on electrocardiography and average of measurements made for five consecutive beats was recorded as

LVEDP for the index patient (**S. Hatipoğlu et al. 2015**).

### Statistical analysis

The data were presented as mean± SD for continuous variables and as percentage for categorical variables. Continuous variables had been compared by unpaired t-test. For non numerical data, Chi – square test had been used.

A P-value of,0.05 was considered statistically significant.

Statistical analysis was performed using the MedCalc 13 Software (Mariakerke, Belgium).

## 3. Results

### Study population:

30 patients referred for catheterization were evaluated; 3 patients were excluded for more than mild valvular disease, 1 for having paroxysmal AF, 3 had LV systolic dysfunction, and 2 were excluded for having insufficient echocardiographic images. The indication for catheterization was coronary artery disease or reevaluation after coronary intervention.

### Patient's characteristics

#### Demographic characteristics:

Mean age of the 21 (9 females and 12 males) patients enrolled was 50.71± 6.18 years. 12 patients were diabetic, 16 were hypertensive, 6 were smoker. Mean LVEDP of patients was 16.85 ± 5.85 mmHg (normal LVEDP in 5 patients and elevated in 16 patients) as it is shown in figure 1

#### Echocardiographic characteristics:

#### 1- Left ventricular end-diastolic diameter (LVEDD):

- The mean LVEDD was 5.140 ± 0.397.
- There was no significant statistical correlation between LVEDD and LVEDP (P value = 0.324).

#### 2-Left ventricular end-systolic diameter (LVESD):

- The mean LVESD was 3.060 ± 0.288.
- There was no significant statistical correlation between LVESD and LVEDP (P value = 0.362).
- See table 1

#### 3- Interventricular septum diameter (IVSD):

- The mean IVSD was 0.820 ± 0.084.
- There was no significant statistical correlation between IVSD and LVEDP (P value = 0.736).
- See table 1

#### 4- Posterior wall diameter (PWD):

- The mean PWD was 0.96 ± 0.114.
- There was no significant statistical correlation between PWD and LVEDP (P value = 0.104).
- See table 1

#### 5- Aortic root diameter:

- The mean Aortic root diameter was 3.36 ± 0.27.
- There was no significant statistical correlation between Aortic root diameter and LVEDP (P value = 0.178).

- See table 1

#### 6- Left atrium diameter:

- The mean left atrium diameter was 3.46 ± 0.76.
- There was no significant statistical correlation between left atrium diameter and LVEDP (P value = 0.989).
- See table 1

#### 7- E (ms):

- The mean E was 89.319 ± 14.238. See table 2
- There was significant statistical correlation between E and LVEDP (P value = 0.019). See table 4

#### 8- Septal S' (cm/s)

- The mean Septal S' was 8.059 ± 2.729. See table 2
- There was no significant statistical correlation between S' and LVEDP (P value = 0.074). See table 4

#### 9- Septal E' (cm/s)

- The mean Septal E' was 7.052 ± 2.315. See table 2
- There was no significant statistical correlation between E' and LVEDP (P value = 0.174). See table 4

#### 10- Septal A' (cm/s)

- The mean Septal A' was 9.13 ± 2.082. See table 2
- There was no significant statistical correlation between A' and LVEDP (P value = 0.322). See table 4

#### 11- Septal E/E' (cm/s)

- The mean Septal E/E' was 13.929 ± 5.12. See table 2
- There was no significant statistical correlation between E/E'and LVEDP (P value = 0.075). See table 4

#### 12- Septal IVCT (ms)

- The mean Septal IVCT was 68.905± 53.75. See table 2
- There was no significant statistical correlation between IVCT and LVEDP (P value = 0.277). See table 4

#### 13- Septal IVRT (ms)

- The mean Septal IVRT was 67.33 ± 17.462. See table 2
- There was significant statistical correlation between IVRT and LVEDP (P value = 0.038). See table 4

#### 14- Lateral S' (cm/s)

- The mean lateral S' was 8.292 ± 1.938. See table 2
- There was no significant statistical correlation between lateral S' and LVEDP (P value = 0.725). See table 4

#### 15- Lateral E' (cm/s)

- The mean lateral E' was 9.923 ± 3.165. See table 2
- There was no significant statistical correlation between lateral E' and LVEDP (P value = 0.789). See table 4

**16- Lateral A' (cm/s)**

- The mean lateral A' was  $11.057 \pm 3.512$ . See table 2

- There was no significant statistical correlation between lateral A' and LVEDP (P value = 0.166). See table 4

**17- Lateral E/E' (cm/s)**

- The mean lateral E/E' was  $10.23 \pm 4.84$ cm. See table 2

- There was no significant statistical correlation between lateral E/E' and LVEDP (P value = 0.166). See table 4

**18- Lateral IVCT (ms)**

- The mean lateral IVCT was  $68.571 \pm 53.330$ . See table 2

- There was no significant statistical correlation between lateral IVCT and LVEDP (P value = 0.072). See table 4

**19- Lateral IVRT (ms)**

- The mean lateral IVRT was  $71.286 \pm 15.599$ . See table 2

- There was no significant statistical correlation between lateral IVRT and LVEDP (P value = 0.325). See table 4

**20- LV-GLS (%)**

- The mean lateral LV-GLS was  $-13.33 \pm 4.902$ . See table 3

- There was no significant statistical correlation between lateral LV-GLS and LVEDP (P value = 0.056). See table 4

**21- SRIVR (1/s)**

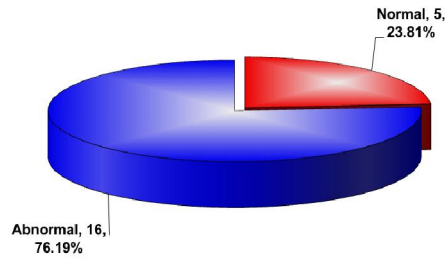
- The mean SRIVR was  $-0.289 \pm 0.256$ . See table 3

- There was no significant statistical correlation between SRIVR and LVEDP (P value = 0.093). See table 4

**22- E/SRIVR**

- The mean E/SRIVR was  $-1156.804 \pm 2561.531$ . See table 3

- There was significant statistical correlation between E/SRIVR and LVEDP (P value = 0.017). See table 4



**Figure 1: Invasive LVEDP**

**Table 1**

|                  | Invasive LVEDP |   |       |          |   |       | T-Test |         |
|------------------|----------------|---|-------|----------|---|-------|--------|---------|
|                  | Normal         |   |       | Abnormal |   |       | t      | P-Value |
|                  | Mean           | ± | SD    | Mean     | ± | SD    |        |         |
| Age              | 52.600         | ± | 8.877 | 50.125   | ± | 5.328 | 0.774  | 0.449   |
| LVEDD (cm)       | 5.140          | ± | 0.397 | 4.888    | ± | 0.508 | 1.012  | 0.324   |
| LVEDS (cm)       | 3.060          | ± | 0.288 | 3.306    | ± | 0.560 | -0.933 | 0.362   |
| IVSD (cm)        | 0.820          | ± | 0.084 | 0.848    | ± | 0.175 | -0.342 | 0.736   |
| PWD (cm)         | 0.960          | ± | 0.114 | 0.837    | ± | 0.147 | 1.706  | 0.104   |
| EF (%)           | 70.400         | ± | 6.427 | 62.188   | ± | 7.360 | 2.235  | 0.038*  |
| Aortic root (cm) | 3.360          | ± | 0.270 | 3.119    | ± | 0.353 | 1.398  | 0.178   |
| LA (cm)          | 3.460          | ± | 0.760 | 3.456    | ± | 0.469 | 0.013  | 0.989   |

**Table 2**

| Descriptive Statistics |       |   |       |   |        |
|------------------------|-------|---|-------|---|--------|
|                        | Range |   | Mean  | ± | SD     |
| E (ms)                 | 64.2  | - | 124   | ± | 14.238 |
| Septal S' (cm/s)       | 4.8   | - | 15.85 | ± | 2.729  |
| Septal E' cm/s)        | 2.8   | - | 13.2  | ± | 2.315  |
| Septal A' cm/s)        | 6.14  | - | 13.3  | ± | 2.082  |
| Septal E/e'            | 7.03  | - | 31.21 | ± | 5.120  |
| Septal IVCT (ms)       | 39    | - | 300   | ± | 53.750 |
| Septal IVRT (ms)       | 44    | - | 106   | ± | 17.462 |
| Lateral S' (cm/s)      | 5.8   | - | 13.7  | ± | 1.938  |
| Lateral E'(cm/s)       | 3.1   | - | 14.8  | ± | 3.165  |
| Lateral A'(cm/s)       | 4.3   | - | 17.8  | ± | 3.512  |
| Lateral E/e'           | 5.6   | - | 26.9  | ± | 4.840  |
| Lateral IVCT (ms)      | 37    | - | 290   | ± | 53.330 |
| Lateral IVRT (ms)      | 53    | - | 106   | ± | 15.599 |

**Table 3**

|             |        |   |        |           |   |          |
|-------------|--------|---|--------|-----------|---|----------|
| LV-GLS (%)  | -22    | - | -5     | -13.333   | ± | 4.902    |
| SRIVR (1/s) | -0.86  | - | -0.006 | -0.289    | ± | 0.256    |
| E/SRIVR     | -12100 | - | -91.28 | -1156.804 | ± | 2561.531 |

**Table 4**Coefficients<sup>a</sup>

| Model       | Unstandardized Coefficients |            | Standardized Coefficients | t      | Sig. |
|-------------|-----------------------------|------------|---------------------------|--------|------|
|             | B                           | Std. Error | Beta                      |        |      |
| (Constant)  | -43.704                     | 23.090     |                           | -1.893 | .131 |
| E wave      | .404                        | .107       | .983                      | 3.784  | .019 |
| Septal Sa   | -1.307                      | .543       | -.610                     | -2.409 | .074 |
| Septal Ea   | 2.856                       | 1.729      | 1.130                     | 1.652  | .174 |
| Septal A    | -.701                       | .620       | -.249                     | -1.129 | .322 |
| Septal E/Ea | 1.663                       | .694       | 1.455                     | 2.397  | .075 |
| Septa IVR   | .433                        | .142       | 1.293                     | 3.052  | .038 |
| Septal IVC  | .106                        | .085       | .977                      | 1.257  | .277 |
| Lateral S   | -.540                       | 1.427      | -.179                     | -.378  | .725 |
| Lateral Ea  | .351                        | 1.231      | .190                      | .286   | .789 |
| lat Aa      | .927                        | .547       | .556                      | 1.693  | .166 |
| Lat E/Ea    | -.431                       | .538       | -.356                     | -.800  | .468 |
| Lat ivc     | -.509                       | .210       | -1.358                    | -2.425 | .072 |
| Lat IVR     | -.105                       | .094       | -.959                     | -1.122 | .325 |
| LVGLS       | .798                        | .299       | .668                      | 2.665  | .056 |
| SIRVR       | -28.164                     | 12.798     | -1.234                    | -2.201 | .093 |
| E/SIRVR     | -.002                       | .001       | -1.047                    | -3.914 | .017 |

a. Dependent Variable: calvedp

#### 4. Discussion

STE is a sensitive tool to evaluate myocardial mechanics and it is independent from translational motion and other through-plane motion effects in contrast to myocardial velocities. Data regarding accuracy, validity, and clinical application of STE are rapidly accumulating (Amundsen BH, et al, 2006; Korinek J, et al., 2005) Since the endocardium is most susceptible to the deleterious effects of interstitial fibrosis and hypoperfusion, the abnormal longitudinal function can be detected at an earlier stage by examining subendocardial function, by means of GLS and SR measurements (Wang J. et al., 2007; Martinez DA. Et al., 2003).

This was done in Echocardiography Unit at Cardiology Department at BAB EL-SHE'RIYA University Hospital – Al-Azhar University – Cairo – Egypt, between January, 2016 to December, 2016.

#### Our results compared with others

Wang et al., 2007 were first to suggest the use of global diastolic SR for the assessment of LV relaxation and filling pressures. Inconsistent with our findings, they reported that global SRIVR derived by STE related well to haemodynamic indices of LV

relaxation both in animal models and in patients. They also stated that SRE was also dependent on LV relaxation in humans and this association was weaker than that of SRIVR. In their study, E/SRIVR predicted LV filling pressures with reasonable accuracy, particularly in patients with an E/Ea ratio of 8 to 15, which is consistent with our findings, those with normal EF, and those with regional dysfunction. Their study included patients with dilated cardiomyopathy and more than mild valvular disease. A number of variables other than LV diastolic function and filling pressures affect mitral inflow, including heart rate and rhythm, PR interval, cardiac output, mitral annular size, and LA function.

We found that SRIVR cannot predict LVEDP inconsistent with S. Hatipoğlu et al, 2015 who found a better predictive value of SRIVR than E/SRIVR. As in patients with coronary artery disease or hypertrophic cardiomyopathy in whom EF is preserved LV filling patterns have a U-shaped relation with LV diastolic function, with similar values seen in healthy normal subjects and patients with cardiac disease. They also reported that SRIVR was a reliable parameter to assess invasively measured LV relaxation



in patients with hypertrophic obstructive cardiomyopathy. They found that SR during the late diastolic filling (SRA) was not related to LVEDP. In addition, they did not find significant correlation between PALS and LVEDP.

Inconsistent with our findings, Kasner et al.(2007) concluded that, in patients with HFpEF, SRIVR cannot predict LVEDP. They also found that STE is accurate in detecting increased LV stiffness, but is not superior to E/E'. In our study E/E'was not correlated with LVEDP.

Despite the fact that, in patients with diastolic dysfunction, the myocardial systolic function of the LV is not preserved, average values of GLS were lower than we would expect in a population with preserved LVEF (Yip G, et al., 2002; Yu CM et al., 2002; Aurigemma GP et al., 2006). Patients enrolled had many risk factors for diastolic dysfunction like diabetes mellitus, hypertension, and coronary artery disease, which may also have resulted in subclinical LV systolic dysfunction (Ng ACT et al., 2009; Pavlopoulos H, et al., 2008; Ernande L, et al., 2011). In patients with diabetes mellitus, it was suggested that GLS deterioration proceeds and/or coexists with LV diastolic dysfunction as a consequence of diabetic cardiomyopathy (Ernande L, et al., 2011). Possibly, other explanation is that GLS reflects predominantly longitudinal motion which is affected more frequently and earlier in the evolution of diastolic dysfunction; however, LVEF is more global or even more a reflection of circumferential contraction (Mor-Avi Vet al., 2011).

### Conclusion

When compared with conventional echocardiographic parameters, other longitudinal strain, and SR indices, SRIVRT independently predicted LVEDP. We suggest that E/ SRIVRT is a valuable parameter to evaluate diastolic function in patients with preserved EF.

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