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Pressure/Volume Ratio as a Simple Parameter for Assessment of left Ventricular Contractile Reserve during Stress Echocardiography

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ABSTRACT

Background: In patients with heart failure, the presence of left ventricular contractile reserve (LVCR) during stress echo (SE) may result in a good response to cardiac resynchronization therapy (CRT).

Aim: To assess the feasibility and accuracy of LVCR by Peak Rest (Systolic Blood Pressure End Systolic Volume) (SPBESV). One can calculate the left ventricular contractile reserve by dobutamine stress echocardiography and assess the correlation of this method to EF related LVCR.

Patients and methods: On 71 patients, this cross-sectional investigation was carried out. They were recommended to perform dobutamine echocardiography either to assess ischemia in those with intermediate pretest probability or to assess viability in those with a kinetic wall motion and with those with low ejection fraction. Every patient underwent a thorough history review, general examination, and local examination. ECG, resting and stress transthoracic echocardiography.

Results: CR Simpson showed a moderate positive significant correlation with the peak-rest EF Simpson in the viability group and moderate positive significant correlation in the ischemic group. While CR m-mode and peak-rest EF m-mode had a significant correlation in the ischemic group and a non-significant one in the viability.

Conclusion: With the two techniques for obtaining the raw ESV values required to calculate Force, LVCR can be estimated with accuracy. While the Simpson approach is more accurate in calculating absolute ESV values, m-mode may also accurately analyse relative (rest-stress) changes. There was no discernible difference between the viable and non-viable groups in terms of LVCR by peak-to-rest ratio in the ischemic and non-ischemic people.

Keywords: Contractile reserve, Stress echo, Heart failure.

INTRODUCTION

The main cause of death worldwide is coronary artery disease (CAD), which continues to claim millions of lives each year despite recent declines in mortality rates in several nations. Therefore, having accurate methods for diagnosis and risk classification is crucial of it [(1)].

The cornerstone of stress echocardiography (SE) for the evaluation of patients with coronary artery disease (CAD) and/or heart failure is the detection of regional wall motion abnormalities (RWMA) (HF) [(2)].

The primary cardiac imaging method for determining the diagnosis and risk of heart disease is stress echocardiography (SE), which is based on the identification of regional wall motion abnormalities (RWMA), stratification of CAD recommended by guidelines [(3)] and also it has a role for determining the myocardial viability and determining whether the myocardium dysfunction would be improved by revascularization [(4)]. The evaluation during times of stress, of the global left ventricular (LV) contractile reserve (LVCR). A load-independent indicator of left ventricular contractile reserve (LVCR) with stress echo is the peak stress/rest ratio of the left ventricle (LV) (SE). [(5)].

For milder inotropic stimuli like dobutamine or exercise stress, the cut-off values for a preserved LVCR are 2.0 and 1.1, respectively. The prognostic "bright side of the force" states that patients with a "strong" heart (normal LVCR values) have a better prognosis than patients with a "weak" heart (reduced LVCR values), and that force-based contractile reserve has a better prognostic value than ejection fraction-based contractile reserve, or RWMA [(6)]. The calculation of force, also known as elastance expressed by the ESP/ESV ratio, is an alternate method. **Suga and Sagawa** [(7)] employed this method in their groundbreaking experimental work. Nowadays, the word force is preferred. Due to its sensitivity to inotropic changes and comparatively high degree of independence from ventricular load, it has been taken into consideration for the evaluation of contractile function [(8)].

Force is expressed as the ratio of peak systolic blood pressure by cuff sphygmomanometer and end-systolic volume (ESV) by 2-D echocardiography [(5)]. Because force does not require the measurement of EDV in addition to ESV, EF is simpler than force [(9)]. Force is more reproducible because EF calls for manually tracing the endocardial contours in two projections at the end of diastole and systole. Any measurement inaccuracy is exacerbated as these values are added together and multiplied to determine the EF. Additionally, it is easier to see the specular endocardial borders at end-systole because myocardial backscatter reflectors lose intensity at end-systole compared to end-diastole. Endocardial borders are more clearly defined towards the conclusion of systole than the end of diastole because of the

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consolidation of the ventricular mass and architecture in systole. Measurements from 2D without contrast are significantly more reproducible for ESV than for EDV [(5)].

Two methods could be used to measure ESV. The gold standard method, known as biplane Simpson (S), calls for integration of the 4-, M-Mode method (T, from parasternal long axis and/or short axis views) with a biplane view of the left ventricle (LV). However, peak stress reduces the likelihood of obtaining images acceptable for volumetric assessment with the S technique, which lowers the quality of the images for elevated heart rate, hyperventilation, and hypercontractility. [(10)].

PATIENTS AND METHODS

71 patients were enrolled in this cross-sectional study, which was carried out at the Cardiology Department, Zagazig University Hospital. They were recommended to perform dobutamine echocardiography either to assess ischemia in those with intermediate pretest probability or to assess viability in those with akinetic wall motions and with those with low ejection fraction.

Inclusion criteria: Patients over the age of 18, those with known or suspected CAD or HF, any level of resting left ventricular function (maintained or diminished), and wall motion imaging by TTE of acceptable quality at rest were all candidates for dobutamine SE.

Exclusion criteria: Patients whose resting acoustic windows for assessing regional wall motion were of unsatisfactory quality and who refused to provide informed consent, significant outflow tract obstruction, severe congenital or primary valvular heart disease, acute coronary syndrome, uncontrolled arrhythmia and severe hypertension were excluded from the study.

All patients underwent thorough history taking, local and general examinations, ECGs, and stress tests as well as transthoracic Echocardiography:

Resting Echocardiography: Utilizing the Modified Simpson method, we measured the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) and M Mode methods. All the studies have been done using GE Vivid E95 Ultrasound Machine with phased array probe transducer M5Sc-D 1.4-4.6 MHz

Stress Echocardiography: All the patients stopped the rate controlling drugs before performing the test by two days. We used starting at 5 and going up to 40 dobutamine mcg/kg/min for the cases for ischemia detection. We used low dose dobutamine starting at 2.5 or 5 mcg\kg\min and increasing to 10 mcg\kg\min at 3-5 min intervals for detection of the viability with co-administration of up to 1 mg of atropine when the patient didn't achieve 0.85 of target heart rate for age at maximum dose. Electrocardiogram and blood pressure were monitored continuously.

Criteria for interrupting the test: Severe chest pain, diagnostic ST-segment shift, excessive blood pressure increase (systolic blood pressure ≥ 240 mmHg, diastolic blood pressure ≥ 120 mmHg), limiting dyspnea, maximal predicted heart rate and significant arrhythmias or limiting side effects.

Volumetric measurements: All volumetric measurements have been obtained according to **ASE** guideline for chamber quantification [(11,12)].

Assessment by biplane method (modified Simpson's rule): We measured LV EDV and ESV calculated by the Simpson biplane method from the apical four. Only representative cycles have the clearest endocardial images. the accepted CR is considered positive by 5-10% increase in ejection fraction.

Assessment using M-Mode: We obtained the linear measurement at or just below the level of the mitral valve leaflets tips of the left ventricular end systolic and end diastolic diameters from 2D images perpendicular to LV long axis. With (peak–rest) (systolic blood pressure–end-systolic volume), we estimated LVCR. The stress-specific LVCR positive criteria were based on prior studies that examined the predictive significance of this parameter: 2.0 for dobutamine.

Ethics approval: Both the Institutional Review Board [IRB] and the Local Committee of Ethics approved the protocol of this research in the Faculty of Medicine, Zagazig University.

Statistical analysis

Microsoft Excel 2016 and the SPSS programme (Statistical Package for Social Sciences) version 26.0 were used to tabulate and statistically analyse the obtained data. Chi square, Mann Whitney, and independent t tests were employed for analysis.

RESULTS

The subjects of our study were divided into two groups according to indication of dobutamine echocardiography: **Group I**: The group for viability detection. **Group II**: The group for ischemia detection. As regards the viability detection group, they were subdivided into two subgroups: **Group Ia**: non-viable and **group Ib**: viable.

There was no significant difference between the two groups as regarding age, sex, diabetes, HTN, CVD, smoking, dyslipidemia and resting and stress condition either heart rate or systolic blood pressure (Table 1).

Table (1): Comparison between non-viable and viable groups regarding demographic and clinical data

		Non-viable N=12		*Viable N=12*		Student Test		P
Demographic data		**X ± SD**		**X ± SD**		**T Test**	**Chi square test**	
Age (years)		62.25 ± 7.71		64.5 ± 7.88		0.707		0.487
BMI (Kg/m^2)		29.98 ± 3.7		30.04 ± 6.33		0.032		0.975
		N	%	N	%			
Gender	**Male**	10	83.3%	10	83.3%		0.000	1.00
	Female	2	16.7%	2	16.7%			
Known diabetic		7	58.3%	6	50.0%		0.168	0.286
Known HTN		8	66.7%	6	50.0%		0.686	0.408
CVD		7	58.3%	7	58.3%		0.000	1.00
Smoking		7	58.3%	8	66.5%		0.178	0.673
Dyslipidemia		5	41.7%	6	45.8%		0.168	0.682
Clinical data		**X±SD**		**X±SD**				
Heart rate (Beat\mins)	**Rest**	81.58± 14.47		75.42± 10.02		1.214		0.238
	peak	125.08± 22.82		123.17± 14.42		0.246		0.808
SBP(mmHg)	**Rest**	119.17 ±14.43		115.83 ±18.32		0.495		0.625
	peak	119.17± 26.79		135.83 ±16.21		1.844		0.079

N) Number, **X**=mean, **SD**=standard deviation, **BMI**=body mass index, **SBP**: systolic blood pressure

There was significant difference between the 2 groups regarding CR (peak\rest) ESP\ESV) by Simpson as CRS in viable group was higher than that of non-viable group and by m-mode as CRM in viable group was higher than that of non-viable group. Also, there was significant difference between the 2 groups regarding peak EF by Simpson as peak EF by Simpson in viable group was higher than that of non-viable group (Table 2).

Table (2): Comparison between the non-viable and viable group as regarding echocardiographic data at rest and peak test

	Non-viable (12)	Viable (12)	Student test		P
			T test	Chi square	
Echo data	X ± SD	X ± SD			
Rest ESV (S)	89.67 ±18.79	77.06± 16.52	1.746		0.095
Rest EDV (s)	148.83±20.18	138.17±24.48	1.165		0.446
EF(simpson) Rest	40.6 ±9.4	43.18 ±11.14	0.61		0.546
EF(simpson) peak	46.68± 9.9	55.68 ± 8.85	2.35		0.028(S)
EF(m-mode) Rest	41.44 ±10.13	42.98± 8.28	0.41		0.687
EF(m-mode) Peak	50.17 ±11.9	57.29 ± 7.46	1.75		0.093
CRS (peak\rest) (SPB\ESV)	1.6± 0.48	2.27 ± 0.69	2.738		0.012(S)
CRM (peak\rest) (SPB\ESV)	1.82 ± 0.41	2.12± 0.23	2.207		0.038(S)

ESV(S): end-systolic volume by Simpson, **EDV(S):** end-diastolic volume by Simpson, **EF:** ejection fraction, **CRS:** Contractile reserve by Simpson, **CRM:** contractile reserve by m-mode, **S:** significant.

Regarding group of ischemia detection, the group is subdivided into two group: **IIa:** negative for detection of ischemia (32). **IIb:** positive for ischemia detection. (15). There was significant difference between the 2 groups regarding hypertension, the hypertension was higher in positive group and diabetes mellitus and the diabetes mellitus was higher in positive group. There was no significant difference between the 2 groups regarding age, sex, smoking, previous CVD and dyslipidemia, heart rate and systolic blood pressure at rest and peak stress (Table 3).

Table (3): Comparison between positive and negative groups regarding demographic and clinical data

		Negative N=32		*Positive N=15*		**Student T Test**		**P**
Demographic data		X± SD		X± SD		Student T	Chi square	
Age (years)		56.28± 8.31		54.2± 7.28		0.831		0.410
BMI (Kg/m^2)		34.49 ± 5.79		34.58 ± 6.59		0.049		0.961
		N	%	N	%			
Gender	**Male**	13	65.0%	7	35.0%		4.473	0.107
	Female	19	70.4%	8	29.6%			
Known diabetic		9	45.0%	11	55.0%		9.519	0.009(HS)
Known HTN		15	55.7%	12	44.3%		4.584	0.032(S)
CVD		5	45.5%	6	54.5%		3.385	.066
Smoking		11	61.1%	7	38.9%		0.653	0.419
Dyslipidemia		13	65%	7	35.0%		0.152	0.696
Demographic data		X± SD		X± SD		Student T	Chi square	
Heart rate (Beat\mins)	**Rest**	71.34± 10.89		73.8± 9.34		0.753		0.456
	Peak	134.66± 8.66		135.8± 6.12		0.460		0.648
SBP (mmHg)	**Rest**	123.75 ±13.62		117.33±10.33		1.616		0.113
	Peak	133.13± 26.69		138±13.20		0.667		0.508

There was no significant difference between the two group regarding ESV by Simpson's at rest, EDV at rest, ejection fraction at rest and at peak by Simpson's and m-mode, and CR by peak\rest (ESB\ESV) Simpson's and m-mode (table 4).

Table (4): Comparison between the positive and negative group as regarding echocardiographic data at rest and peak test

		Negative N=32	*positive N=15*	**Student T Test**		**P**
				T Test	**Chi square test**	
Echocardiographic data						
Rest ESV (S)		32.62 ± 10.08	28.97 ±13.32	1.041		0.304
Rest EDV(S)		72.14± 16.04	72.33± 11.29	0.042		0.966
EF (Simpson)	**Rest**	65.16 ± 5.07	62.62 ± 6.67	1.446		0.155
	Peak	77.5 ± 6.6	75.85 ± 8.83	0.719		0.476
EF (M-mode)	**Rest**	65.2 ± 6.04	65.52 ± 8.32	0.151		0.880
	Peak	77.66 ± 5.79	78.77 ± 6.44	0.608		0.546
CR(peak\rest(SPB\ESV) Simpson		2.26 ± 0.81	2.43 ± 1.15	0.604		0.548
CR(peak\rest(SPB\ESV) m-mode Simpson		2.46 ± 0.99	2.51 ± 0.91	0.183		0.856

CR Simpson showed a moderate positive significant correlation with the (peak-rest) EF Simpson in the viability group and moderate positive significant correlation in the ischemic group. While CR m-mode and (peak-rest) EF m-mode had a significant correlation in the ischemic group and a non-significant one in the viability (Table 5).

Table (5): correlation between CR by peak\rest (SBP\ESV) and CR by peak-rest EF in viability and ischemic group

		CR peak\rest (SBP\ESV)	
		R	**P –value**
Viability	**(Peak-rest) EF m-mode**	**0.349**	**0.095**
	(Peak-rest) EF Simpson	**0.442**	**0.031**
Ischemia	**(Peak-rest) EF m-mode**	**0.299**	**0.041**
	(Peak-rest) EF Simpson	**0.422**	**0.003**

Receiver operating characteristic (ROC) analysis was performed to determine diagnostic value of different parameters in predicting viability. Peak-rest (ESB\ESV) Sim could discriminate between non-viable and viable results at cutoff 2 with sensitivity and specificity were 75%, and 92% respectively (p<0.001). Peak-rest (ESB\ESV) M-mode could discriminate between non-viable and viable results at cutoff 1.9 with sensitivity and specificity were 83%, and 75% respectively (p<0.005). Standard CR by Simpson could discriminate between non-viable and viable results at cutoff 4.5 with sensitivity and specificity was 83%, and 58% respectively (p=0.002). Standard CR by M-mode could discriminate between non-viable and viable results at cutoff 7 with sensitivity and specificity was 91%, and 67% respectively (p=0.022) (Table 6).

Table (6): Validity of different parameters in predicting viability

	Cutoff value	AUC	Sensitivity	specificity	Accuracy	P value
CR Sim	2	0.819	75%	92%	94%	0.001
CR m-mode	1.9	0.781	83%	75%	92%	0.005
Standard Sim	> 4.5	0.788	83%	58%	97%	0.002
Standard m-mode	>7	0.747	91%	67%	90%	0.022

CR (Peak-rest (ESB\ESV) Sim could discriminate between ischemic and non-ischemic results at cutoff 2.3 with sensitivity and specificity was 60%, and 56% respectively (p<0.748). CR (Peak-rest (ESB\ESV) M-mode could discriminate between ischemic and non-ischemic results at cutoff 2 with sensitivity and specificity was40%, and 43.8% respectively (p<0.859). Standard Sim (Peak-rest) EF by Simpson could discriminate between ischemic and non-ischemic results at cutoff 17.5 with sensitivity and specificity was 30%, and 88% respectively (p=0.099). Standard (Peak-rest) EF by M-mode could discriminate between ischemic and non-ischemic results at cutoff 14.3 with sensitivity and specificity was 50%, and 70% respectively (p=0.419) (table 7).

Table (7): Validity of different parameters in predicting ischemia

	Cutoff value	AUC	Sensitivity	Specificity	Accuracy	P value
CR Sim	2.3	0.529	60%	56%	68%	0.748
CR m-mode	2	0.517	40%	43.8%	67%	0.859
Standard Sim	17.50	0.513	30%	88%	70%	0.099
Standard m-mode	14.3	0.580	50%	70%	77%	0.419

DISCUSSION

Our study was based on non-intrusive pressure and volume measurements. The primary finding of the study was that Peak\rest (ESV/SBP) is feasible, less time consuming and doesn't rely on measurement of EDV when under dobutamine stress. This relatively straightforward global contractility index did not influence imaging time and only slightly increased the time required for off-line analysis. It enabled the uncovering of very diverse and variable patterns of contractility reserve that underlie a certain ejection fraction at rest.

The myocardium's innate ability to contract regardless of changes in the pre-load or afterload is known as contractility. Despite measurement issues, contractility is still a crucial notion for separating the impacts of a primary change in loading conditions from an intrinsic change in the force of contraction.

When using dobutamine, the force-frequency relationship and the impact of inotropic stimulation are both taken into account when evaluating PVR.According to earlier research, LVCR based on force is easier, quicker, and more effective for risk categorization than EF. Because it does not need for the measurement of EDV needed in addition to ESV for EF, it is simpler computationally. Because EF calls for manually tracing the endocardial contours in two projections at end-diastole and end-systole, it is more repeatable. Any measurement error is compounded as these values are added and multiplied to generate EF, which is determined using EDV and ESV estimates using the formula: ESV (EDV ESV)/EDV [(13)].

In our study we found that regarding the group for ischemia detection ROC curve analysis data indicated that when 2.3 cutoff value was used, the LVCR by Simpson method for diagnosing of ischemia could achieve a sensitivity of 60% and specificity of 56%. As regards the viability when 2 cutoff value was used, the LVCR by Simpson method for diagnosing of viability could achieve a sensitivity of 75% and specificity of 92%. **Bombardini *et al.*** [(14)] found that the sensitivity of abnormal LVCR for CAD detection was 55.7% (95% CI 45.2% to 65.8%) with 66.8% (95% CI 62.6% to 70.7%) specificity. f RWMA and/or abnormal LVCR were considered, sensitivity rose to 72.2% (95% CI 62.1% to 80.8%) and specificity fell to 65.8% (95% CI 61.6% to 69.8%) this difference could be explained as this results from all patient in this study in which they used different method for stress echo-cardiography as dipyridamole, exercise and dobutamine.

In our study it was easy to assess SBP in manual way before starting dobutamine infusion and also at the end of dobutamine, we also could measure it during the test and in each stage of the dobutamine infusion we also assess ESV in all patients with two methods M-mode and Simpson's without interruption of the analysis time, endocardial border could be well seen and detected in ESV in all patients.

In our study we found that LVCR by Peak\rest ratio was higher in viable group than in the non-viable group and this could be explained that viable myocardium may be hibernating or stunning and retain some contractile reserve that appeared with infusion of dobutamine in contrast to non-viable one with scared or fibrotic myocardium and no change occurred at peak stress with no retaining of any contractile reserve.

This is consistent with Several studies confirmed that LVCR is decreasing in falling heart (the patient with LV dysfunctional and reasonably during dobutamine stress Echo in which we used dobutamine as beta1 agonist to stimulate heart if it fail to increase contractile reserve [(15)]. Also, this is consistent with **Bombardini *et al.*** [(14)] in which they found that the abnormal LCVR increased with lack of viability

In our study, there was no significant relationship regarding Peak\rest LVCR between ischemic and normal people with CR Sim was 2.26 ± 0.81 in normal people and 2.43 ± 1.15 in ischemic people with p value 0.548 and this is because the contractile reserve in ischemic people could be determined by many other factors like the extent of CAD if single or multiple vessels disease and\or duration of chronic ischemic heart disease. **Bombardini *et al.*** [(14)] assessed CR by the peak\rest ratio LVCR with ESV divided over the body surface area was 10.93 ± 4.56 in normal individual and 5.56 ± 6.35 in patients with CAD and 1.32 ± 2.17. This difference may be because of the small number of the studied people in our study (15 with ischemic response vs 45) also ESV was indexed by body surface area.

Grosu *et al.* [(16)] built PVR (pressure \volume relationship) in 137 patients with dobutamine echo-cardiography. In 27 individuals, the resting EF was normal; in 110 patients, it was abnormal. Normal resting EF patients typically have aberrant biphasic response (slight increase at the beginning of the stress then decrease of PVR), and many patients who had abnormal resting EF also had normal PVR.

The biphasic response that was found in 27 out of 50 (54%) patients with positive stress echo and in 31 out of 87 (36%) patients with negative stress echo was the definition of the PVR (x2 P 0.05).

As regarding Echocardiographic parameters to predict contractile reserve during dobutamine echocardiography, in our study, we found that there was statically difference in between the viable and non-viable group as regarding the peak ejection fraction as the viable group has higher peak EF with (p value 0.028). We found

since the left ventricular assessment revealed no statistically significant difference in contractile reserve in viability detection group. As regards resting ESV assessed by Simpson method with (p value 0.095) between viable and non-viable myocardium. This may be because the amount of hibernating myocardium and or scar tissue not usually affected at the baseline and mostly the difference appears after infusion of dobutamine with the increase of blood flow to viable parts of myocardium.

Other studies found different methods to asses LVCR like **Magdy *et al.*** [17] assessed using MAPSE (Mitral annular plane systolic excursion) in 50 patients with ischemic cardiomyopathy, it was discovered that contractile reserve was substantially correlated with EF at rest and low-dose dobutamine ($r = 0.283$, $p = 0.046$ and $r = 0.348$, $p = 0.013$, respectively).

As regards correlation between EF related LVCR and Peak\rest LVCR using M-mode and Simpson's methods in our study, we found the evaluation of contractile capacity in correlation with EF related LVCR using Simpson method was more significant than assessment by M-mode with P value 0.003. While, it was 0.041 by M –mode in the ischemia group and this could be explained as that there are many disadvantages of M-mode used in assessment of ESV as there is regional variation in ventricular shape and function where it only offers details on dimension and contractility along a single line, and it is associated with many types of acquired heart disease, particularly coronary artery disease. This could either overstate the abnormality if the M-mode beam exclusively transits the wall motion anomaly, or it could underestimate the level of global dysfunction if only a normal region is interrogated. While, in Simpson method we assessed volumetric measurement including all the wall of the ventricles.

In our study, there was significant correlation as regards the CR and standard method in viability detection group. With **Torres *et al.*** [5]**,** the association was moderate for both S and m-mode when taking into account LVCR (based on relative changes between rest and stress) ($n = 100$, $r = 0.899$, p 0.01). **Bombardini *et al.*** [14] found that at individual patient analysis, 966 patients with EF-based LVCR showed abnormal force-based LVCR, and 357 patients without EF-based LVCR showed normal force-based LVCR. Overall, there was a good correlation between LVCR as measured by EF and force. 72.5% %.

Atherosclerotic factors such as DM, HTN, smoking, dyslipidemia, CVD, sex and advanced age were found to be independent determinant of the presence of positive results of ischemia either by imaging or by coronary angiography not only that but also it's used to determine the predictive atherosclerotic events in the coming days [18]**.**

In our study we found that, cardiovascular risk factors such as DM and HTN were more common in ischemic group than those with negative dobutamine stress echo with p value was 0.009 as regarding DM and p value was 0.032 as regarding HTN. But other risk factors such as smoking, dyslipidemia and CVD are non-significant as this may be because of the small number of the ischemic people within the studied group.

CONCLUSION

With the two techniques for obtaining the raw ESV values required to calculate Force, LVCR can be estimated with accuracy. While the Simpson approach is more accurate in calculating absolute ESV values, m-mode may also accurately analyse relative (rest-stress) changes. In the viable group, LVCR by peak-rest ratio is higher than in the non-viable group with no significant difference between the ischemic and non-ischemic people.

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