

ORIGINAL ARTICLE

Strain Magnitude Assessed at Rest and During Stress Echocardiography in Patients with Normal Coronary Flow Reserve

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Abstract

Background: Coronary flow and myocardial contractile performance assessed by strain magnitude increase during a dobutamine stress echocardiogram (DSE). Normal coronary flow reserve (CFR) can be attained upon completion of a DSE at age-predicted maximum heart rate (HR) ($HR_{max} = 220 - \text{age}$) or submaximal HR [(0.85) HR_{max}] or before completion (early CFR).

Objective: To ascertain the association between delta strain and HR in patients with early normal CFR.

Methods: This prospective study included patients whose normal CFR was obtained before the DSE was completed. Percentage of resting HR ($\%HR_{rest} = [(HR_{rest} \div HR_{max}) 100]\%$) and $\%HR$ CFR = $[(HR \text{ at the time of CFR attainment}) \div (HR_{max}) 100]\%$ were recorded. Strain was assessed in the left ventricular region of interest, and delta strain was calculated as the difference between the measures obtained at HR_{rest} and after the DSE was completed. Strain agreement analysis for HR_{rest} , $\%HR_{rest}$, and $\%HR$ CFR was performed using the kappa coefficient. The Shapiro-Wilk test was used to assess data normality, and the Mann-Whitney test was used to compare the groups. A p-value < 0.05 was considered statistically significant.

Results: Strain measured $-23.3\% \pm 4.3\%$ at baseline and $-31.1\% \pm 4.9\%$ during the DSE. In delta strain > 8 absolute points, the ROC curves showed an area under the curve of 0.874 ± 0.07 for $\%HR_{rest}$ ($p = 0.001$) and an area under the curve of 0.862 ± 0.07 for $\%HR$ CFR ($p = 0.001$). In delta strain > 8 points, $\%HR_{rest} \leq 42.6\%$ of HR_{max} and $\%HR$ CFR $\leq 62.5\%$ of HR_{max} showed an accuracy of 82.9% and 79.8%, respectively.

Conclusion: In this study, lower HR_{rest} and HR at the time of CFR attainment had a good association with better myocardial contractile performance, according to the change in strain magnitude.

Keywords: Blood Flow; Blood Flow Velocity; Myocardial Contraction Strain; Echocardiography, Stress/methods; Vasodilatador Agents; Cardiotonic Agents; Coronary Artery Disease; Diagnostic, Imaging/methods.

Introduction

Myocardial deformation measurement from echocardiographic strain is an important tool for assessing global or segmental performance of the cardiac muscle.¹⁻⁵ Strain may be revealing of a healthy myocardium with contractile reserve or a myocardium whose performance is compromised.⁶⁻⁸

Adenosine and dipyridamole are coronary vasodilators that may exert a positive inotropic effect on the myocardium. Thus, these drugs can be used to assess strain changes, myocardial contractile reserve, and coronary flow reserve (CFR).^{9,10} However, dobutamine is a potent positive inotropic agent and has a coronary vasodilator effect similar to that of adenosine or dipyridamole. Consequently, it better expresses myocardial contractile reserve on strain and allows a simultaneous assessment of CFR.¹¹⁻¹⁷

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Normal CFR can be attained upon completion of a dobutamine stress echocardiogram (DSE), or even at a lower heart rate (HR) than predicted for completion of the test (early CFR).^{15,18-22} Additionally, we have observed in practice that vigorous contractile responses during the DSE can be detected in patients with lower resting HR (HR_{rest}) and in those in which normal CFR is attained at lower HRs. The actions of dobutamine, potentiated by the Gregg effect, are relevant to justify the intensity of left ventricular (LV) contractile response at low HRs, although other factors may modulate this response and contribute to its intensity.²³

We aimed to ascertain the correlation of HR recorded at baseline and at the time of CFR attainment with the magnitude of strain change during the DSE in patients with early normal CFR.

Methods

A convenience sample of 29 patients referred for DSE with known or probable coronary artery disease was included. This prospective study evaluated patients whose normal CFR was obtained before the DSE was completed. Cases of sinus rhythm, controlled blood pressure, good echocardiographic window, preserved LV ejection fraction (Simpson method), and normal LV segmental contraction in the left anterior descending artery (LAD) territory at rest and during stress were included. Valvulopathy, if present, should not be more than mild.

An E9 ultrasound system (GE Healthcare, Milwaukee, Wisconsin, USA) equipped with an M5S transducer was used in the study. LV segmental contraction was assessed at baseline and during stress, and contractile deformation was determined by peak systolic strain measured by Doppler. Absolute change in strain, considering values at HR_{rest} and immediately after submaximal HR on DSE, constituted the delta strain. After the delta strain cutoff point was defined in statistical analysis for comparison of two groups, the correlation between strain and HR was performed.

HRs were recorded as absolute values and percentages of age-predicted maximum HR (HR_{max}). HR_{max} (calculated as 220 - age in years) and submaximal HR (85% of HR_{max}) predicted for each case during the DSE were considered.^{11,12}

Then, %HR_{rest} = [(HR_{rest} ÷ HR_{max}) 100]% and %HR CFR = [(HR at the time of CFR attainment) ÷ (HR_{max})100]% were established.

During the DSE, quad screen images included recordings of baseline measurement, low-dose dobutamine (up to 20 µg.kg⁻¹.min⁻¹), maximum dose, and the recovery phase. A continuous dobutamine infusion was administered into a peripheral vein at increasing doses of 10, 20, 30, and up to a maximum of 40 µg.kg⁻¹.min⁻¹, if necessary, at 3-minute intervals. At the beginning of the third stage (30 µg.kg⁻¹.min⁻¹), a bolus of atropine (0.25 or 0.50 mg) was administered up to a maximum cumulative dose of 2 mg, if indicated, in order to complete the test (Figure 1). Upon completion of

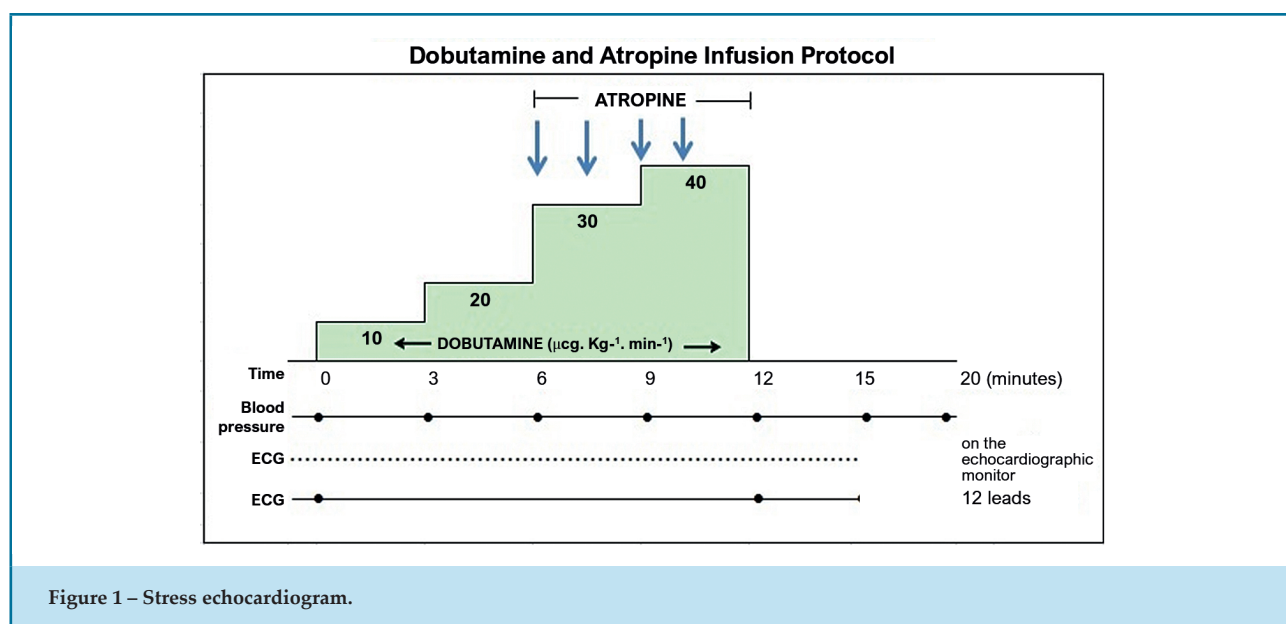


Figure 1 – Stress echocardiogram.

the DSE, submaximal HR was reached and/or myocardial ischemia was determined. However, the case would be excluded if ischemia occurred before the recommended HR was reached. Ischemia was characterized by the appearance of a contractile abnormality or by a worsening pre-existing contractile abnormality. The LV was divided into 16 segments, and the contraction could be defined as normal, hypokinesia, akinesia, and dyskinesia. After completion of the test, all patients were given a bolus of 30 to 60 mg of intravenous esmolol to return HR to baseline levels. In case of intolerance or occurrence of an adverse effect with potential risk to patient safety, the test would be interrupted.^{11,12}

During apical 2-chamber recording of the LV, after smooth sliding and/or tilting of the transducer, the mid-distal segment of the LAD was visualized as a tubular and reddish image on color Doppler. The pulsed wave Doppler beam was positioned as parallel as possible, with the smallest sample volume (2 mm) placed in the LAD, and then peak diastolic flow velocity was measured. This measurement was performed at baseline and intermittently during the DSE, so that normal CFR (≥ 2) was attained before completion of the test. Based on the literature, CFR was calculated by dividing peak diastolic flow velocity obtained during the DSE by that recorded at baseline.^{14,16,18,21,22,24}

The aortic flow was recorded by conventional pulsed wave Doppler, with systole delimited by the period between the R wave on electrocardiogram and valve closure on Doppler. Subsequently, the center of the color tissue Doppler cone beam was placed as parallel as possible to the anterior wall of the LV, in the apical 2-chamber position. The tissue Doppler cone sector angle was kept as small as possible to obtain a loop with the highest frame rate (169 frames per second) of the system, favoring the recording of a greater amplitude of longitudinal displacement of the myocardium during systole and, consequently, a higher strain.^{1,3,6,7} At baseline, the strain Doppler sample was positioned in the myocardium and close to the level at which the LAD flow had been recorded. Then, the highest systolic strain was measured in this region of interest with the respective recording HR. Soon after submaximal HR was reached in the test, a new strain Doppler loop was stored, and this strain measurement was performed upon completion of the DSE.

Statistical analysis

Descriptive data analysis was performed using tables and charts, with continuous variables presented as median and interquartile range and categorical variables expressed as absolute frequencies and percentages. The estimated cutoff point defined by the mean or median or quantiles for change in absolute strain (delta strain) was obtained by studying the distribution of these parameters from a total set of 200 samples of size 29, resampled from the dataset by the Bootstrap method. Using the delta strain parameter as the gold standard, a cutoff point was determined by the ROC curve for HR_{rest}, %HR_{rest}, and %HR CFR, and the correlation between these variables and strain magnitude was assessed. Strain agreement analysis was performed for HR_{rest}, %HR_{rest}, and %HR CFR using the kappa agreement index. The Shapiro-Wilk test was used to assess the normality of the distribution of quantitative variables, and the nonparametric Mann-Whitney test was used to compare the delta strain parameter groups in relation to the distribution of quantitative variables. Intraobserver variability and interobserver variability of strain measurements were assessed by the Spearman correlation coefficient and the intraclass correlation coefficient, respectively. In all tests, p-values lower than 0.05 were considered statistically significant. Analyses were performed with SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

In the group of 29 patients (19 men), the mean age was 62 ± 12 years. There were 20 (69%) patients with hypertension, 18 (62%) with dyslipidemia, 8 (28%) with diabetes, and 5 (17%) with known coronary artery disease.

Strain Doppler measurement in the region of interest ranged from $-23.3\% \pm 4.3\%$ at baseline to $-31.1\% \pm 4.9\%$ during stress. The delta strain cutoff point measured 8 absolute units, which was used to define Group I (delta strain > 8) and Group II (delta strain ≤ 8).

In the groups, patients had preserved LV ejection fraction and reached high HR_{max} levels, with different levels of %HR_{rest} and %HR CFR. Early normal CFR was recorded with low-dose dobutamine in 93% of Group I patients and in 53% of Group II patients (Figure 2). However, early normal CFR was obtained before the maximum dose of dobutamine in all patients (Table 1).

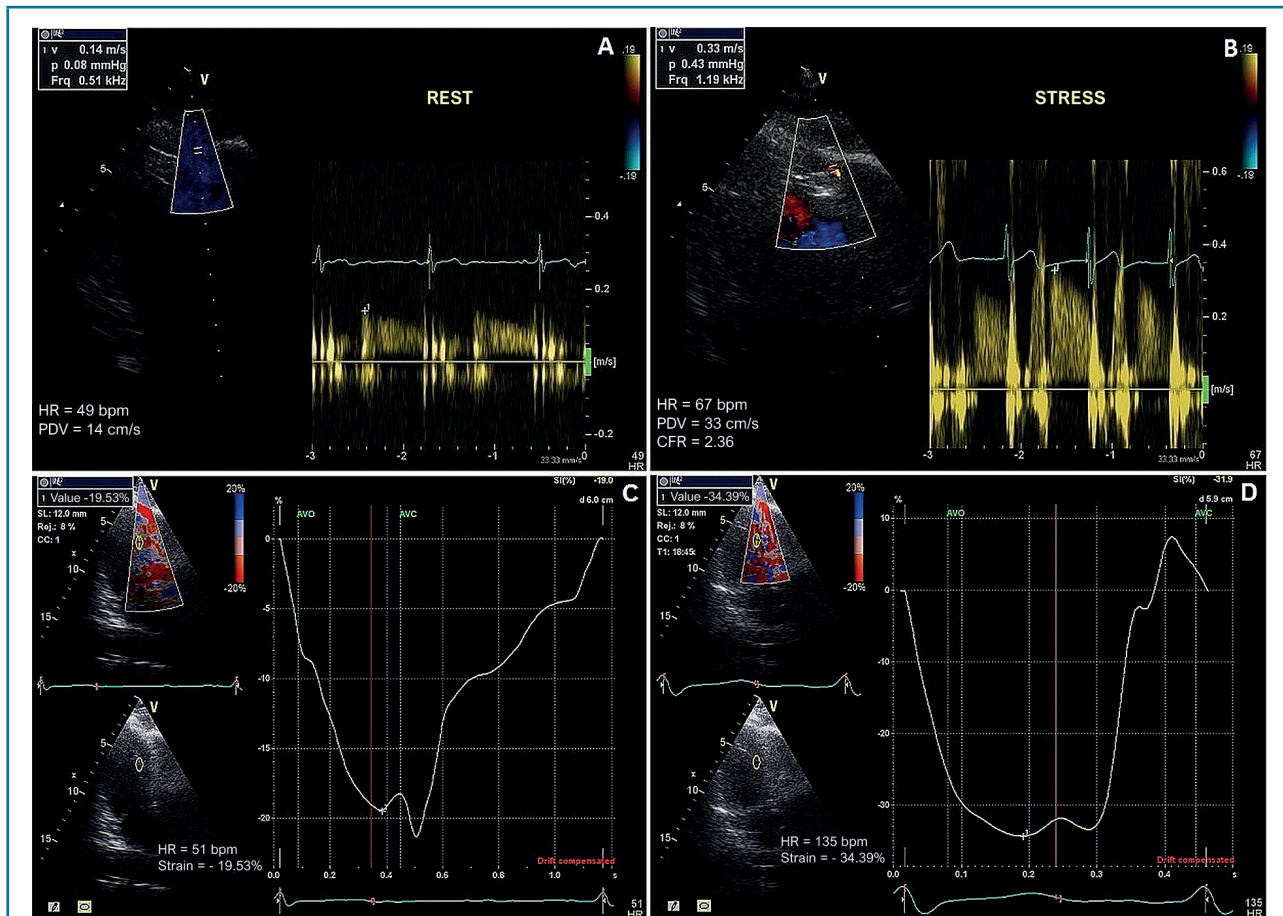


Figure 2 – A 60-year-old patient with a predicted maximum heart rate (HR) of 160 bpm on stress echocardiogram. Peak diastolic velocity (PDV) of left anterior descending artery (LAD) flow at baseline (A) and during stress (B). Early normal coronary flow reserve (CFR = PDV during stress ÷ PDV at rest) was attained with HR = 67 bpm (42% of maximum HR predicted for the test). Doppler-derived strain in the LAD territory measured -19.53% at rest (C) and -34.39% after submaximal HR was reached during stress (D), resulting in a change of 14.8 absolute points.

There was no difference between the groups regarding ventricular mass and left atrial volume. The E/E' ratio was used as the reference for assessing LV filling pressure and did not differ between groups. Peak diastolic flow velocity in the LAD in Group I was lower both at rest and during stress. The double product in Group I was lower at baseline, but the groups did not differ during stress (Table 2). The positive cases for myocardial ischemia (two in each group) did not compromise the LAD territory and were maintained in the study because they occurred after submaximal HR was reached in the test. There were no limiting symptoms, arrhythmias, or relevant adverse effects.

Delta strain associations with HR levels were analyzed according to the ROC curve (Figure 3), with good accuracy for HR_{rest} , $\%HR_{rest}$, and $\%HR$ CFR (Table 3). Based on the kappa coefficient, the results for absolute

delta strain (> 8 or ≤ 8) showed a regular agreement with a tendency to good agreement for HR_{rest} , and a good agreement with a tendency to very good agreement for $\%HR_{rest}$ and for $\%HR$ CFR (Table 3).

Strain measurements were performed by two independent observers in the same echocardiographic loop of 10 patients, and the measurements were repeated by the same observer after 30 days. The analysis of the Spearman correlation coefficient and the intraclass correlation coefficient demonstrated high intraobserver and interobserver reproducibility (Table 4).

Discussion

Our study assessed myocardial contractile performance in patients with normal CFR obtained before completion

Table 1 – Measurements during baseline and stress echocardiogram

Variables		Delta strain	Number of patients	Median	Interquartile range
LVEF (%)	(baseline)	> 8	14	56	39.5-75.5
		≤ 8	15	59	41-73
HR (bpm)	(resting)	> 8	14	60	24-96
		≤ 8	15	71	50.5-86.5
	(DSE)	> 8	14	152	140.0-166.0
		≤ 8	15	152	131.5-167.5
%HRrest		> 8	14	37.62	21.47-53.16
		≤ 8	15	45.07	32.68-59.31
%HR CFR		> 8	14	47.34	20.53-81.27
		≤ 8	15	68.02	17.5-130.41
Measurements when CFR (≥ 2) is attained on DSE					
10 (μcg.kg ⁻¹ .min ⁻¹)		> 8	6		
		≤ 8	5		
20 (μcg.kg ⁻¹ .min ⁻¹)		> 8	7		
		≤ 8	3		
30 (μcg.kg ⁻¹ .min ⁻¹)		> 8	1		
		≤ 8	7		

Delta strain: difference between strain measures during stress and at baseline; LVEF: left ventricular ejection fraction; HR: heart rate; bpm: beats per minute; DSE: dobutamine stress echocardiogram; %HR: percentage of HR in relation to maximum HR predicted for the test; %HRrest: percentage of resting HR in relation to maximum HR; CFR: coronary flow reserve; %HR CFR: percentage of HR at the time of CFR attainment in relation to maximum HR.

of the DSE using Doppler-derived strain, which was chosen as a research tool for some reasons. It allows the recording of a higher rate of myocardial deformation than two-dimensional strain, as long as the radial component is minimized and the longitudinal Doppler recording is optimized. Also, Doppler-derived strain of a specific region may be more feasible at very high HRs.^{1-3,6,7,25}

Two-dimensional strain for multisegmental assessment of the LV is more reproducible than Doppler-derived strain.^{1,2,7,26} However, we demonstrated that Doppler-derived strain is a reliable option in a specific segmentation, with high intraobserver and interobserver reproducibility.

According to the ROC curve and the delta strain cutoff point, the accuracy of HRrest, %HRrest, and %HR CFR for detecting an increase in delta strain magnitude by more than 8 absolute points was observed. HRrest was

found to be important, but the correlation with age-predicted HRmax was more relevant in this study, since %HRrest and %HR CFR showed better accuracy, which was confirmed by the kappa coefficient analysis.

During the DSE, it is possible to observe a progressive increase in peak diastolic flow velocity in the LAD and determine the time point at which normal CFR is attained. This showed that %HRrest and %HR CFR were lower in Group I, demonstrating the early and important vasodilator effect of dobutamine, since atropine was not used at the initial stages.

Dobutamine acts on the myocardium and coronary arteries mainly by activating the adrenergic receptor system. Activation of β1 receptors increases inotropism, while activation of β1 and β2 receptors promotes flow increase by direct action on epicardial coronary arteries and microcirculation.²⁷⁻²⁹

Table 2 – Analysis of echocardiographic variables at rest and during stress

Variables	Delta strain	Median	Interquartile range	p
LV mass/BSA	> 8	91.56	31.66-142.64	0.847
	≤ 8	88.17	22.22-152.50	
LA volume	> 8	45.00	16.5-78.5	0.310
	≤ 8	43.00	26.5-62.5	
LA volume/BSA	> 8	25.57	11.7-39.23	0.377
	≤ 8	24.18	7.77-39.5	
E wave	> 8	7.00	5.5-9.5	0.621
	≤ 8	7.00	3.4-13.0	
E/A ratio	> 8	1.12	0.32-1.96	0.085
	≤ 8	1.00	0.22-1.70	
E' wave	> 8	0.80	0.36-1.26	0.425
	≤ 8	0.70	0.15-1.35	
E/E' ratio	> 8	8.75	1.62-17.10	0.252
	≤ 8	10.00	-0.56 -21.67	
PDV in LAD (baseline)	> 8	18.50	7.00-33.00	0.038
	≤ 8	26.00	10.00-49.00	
PDV in LAD (DSE)	> 8	39.50	10.38-75.38	0.046
	≤ 8	54.00	10.50-94.50	
Double product (baseline)	> 8	7490.00	3832-11272	0.005
	≤ 8	8520.00	6565-11245	
Double product (DSE)	> 8	24720.00	21007-28987	0.780
	≤ 8	24480.00	17200-33200	

Delta strain: difference in change from rest to stress; LV: left ventricle; BSA: body surface area; LA: left atrial; E wave: Doppler flow of the mitral valve; E' wave: tissue Doppler of the mitral valve; PVD: peak diastolic velocity; LAD: left anterior descending artery; DSE: dobutamine stress echocardiogram; double product: systolic blood pressure multiplied by heart rate.

Westerhof et al.,²³ described that increased coronary perfusion through the Gregg effect modifies myocardial contractility and oxygen consumption under resting conditions. According to this effect, increased coronary flow results in the opening of ion channels, determining a greater supply of intracellular calcium, followed by additional calcium sensitization of the contractile muscle apparatus. This mechanism of direct proportionality between diastolic perfusion, supply, and calcium sensitization for contractility may be another contributor to exacerbation of delta strain magnitude during dobutamine use, even at low doses. This is consistent, for example, with our finding of normal CFR with %HR CFR

below 40% of predicted HRmax on DSE. Also, patients with lower HRs have a longer diastolic period, which also favors coronary flow supply.

Administration of dipyridamole or adenosine shows the correlation between normal CFR and myocardial contractile response based on strain; however, this response is less pronounced than that of dobutamine.^{9,10} A study conducted by Takeuchi et al.,¹⁴ offered the prospect of dobutamine use for CFR assessment. This is the most commonly used stressor in echocardiography, and, because of its potent vasodilator effect, it provides additional information related to myocardial contractility and regional flow reserve. Our study found that normal

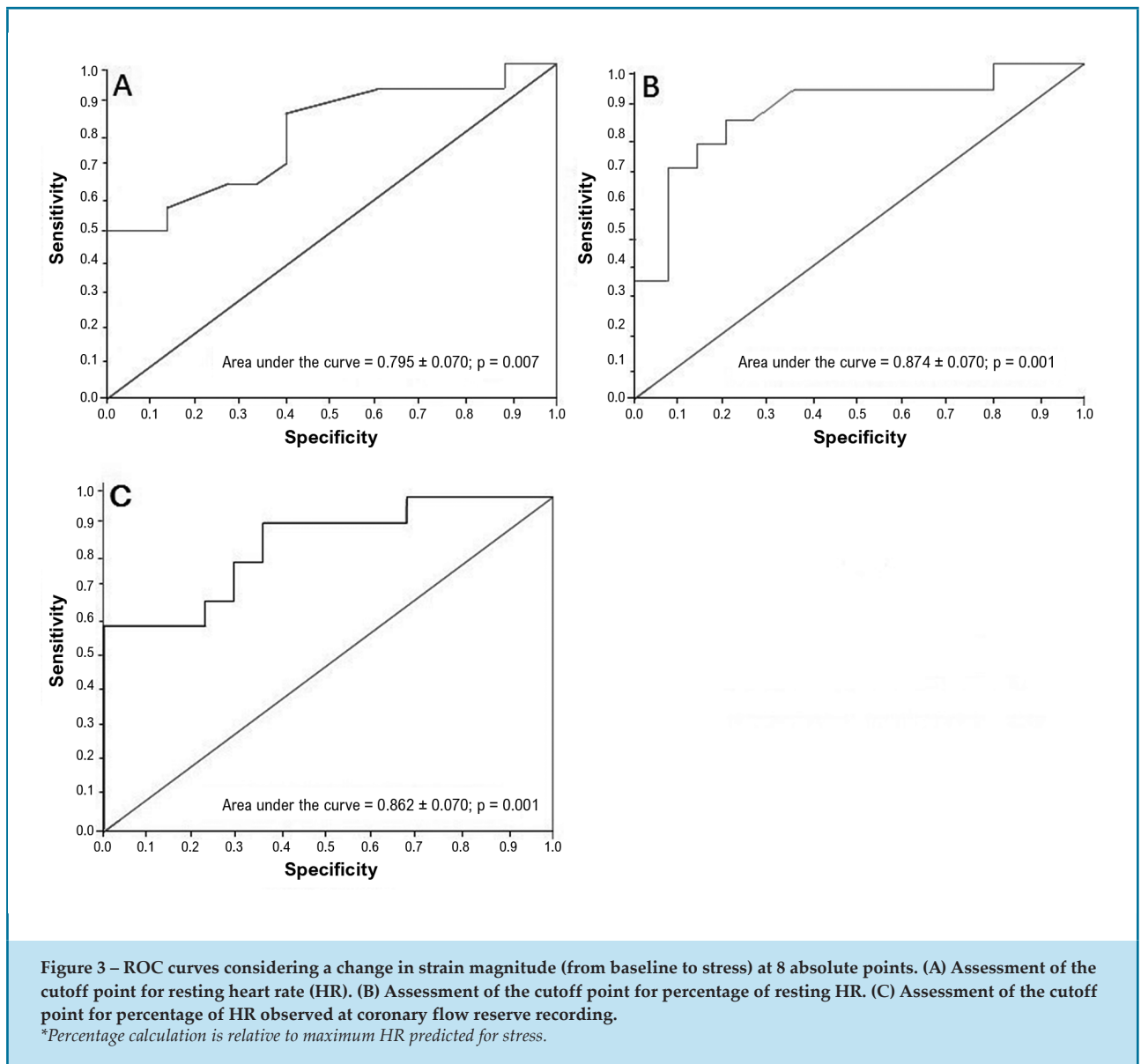


Table 3 – Accuracy, kappa coefficient, and other parameters considering a delta strain cutoff point higher than 8 absolute points

Variables	value	Sensitivity		Specificity		PPV	NPV	Accuracy	Kappa coefficient
		%	95% CI	%	95% CI				
HRrest	≤ 70 bpm	85.7%	64.7%-100%	60.0%	31.9%-88.1%	68.2%	80.8%	72.9%	0.453±0.159
%HRrest	≤ 42.6%	85.7%	64.7%-100%	80.0%	57.1%-100%	81.1%	84.8%	82.9%	0.656±0.140
%HR CFR	≤ 62.5%	92.9%	77.4%-100%	66.7%	39.6%-93.7%	73.6%	90.3%	79.8%	0.590±0.144

PPV: positive predictive value; NPV: negative predictive value; bpm: beats per minute; HR: heart rate; %HR: percentage of HR in relation to maximum HR predicted for the test; %HRrest: percentage of resting HR in relation to maximum HR; %HR CFR: percentage of HR at the time of CFR attainment; CFR: coronary reserve.

Table 4 – Intraobserver and interobserver variability of strain measurements by Spearman and intraclass correlation coefficient analyses

	Observer A – Measurement 2		Observer B – Measurement 1	
	ρ_{Spearman}	95% CI	$\rho_{\text{intraclass}}$	95% CI
Observer A - Measurement 1	0.977	0.944-0.996	0.894	0.622-0.971
Observer A - Measurement 2	-	-	0.938	0.770-0.983

CFR was a precursor of normal contractility, culminating in a negative DSE for ischemia in the LAD territory.

Fortes et al.,²⁰ reported that normal CFR can be recorded in patients with a negative DSE for ischemia before the recommended target HR for the completion of the test. Another study showed that patients with normal CFR attained before the target HR had a better prognosis over a mean follow-up period of 28 months.²² Considering CFR recording before completion of the DSE, we studied the prospect of a better contractile performance, which was observed and associated with lower HRs.

Clinical implications

We observed in this study that dobutamine had a major coronary vasodilator action, which allows attaining normal CFR even at low doses and correlating it with a significant contractile reserve. A good association between lower HR and better myocardial contractile performance was found, and it is interesting to highlight that athletes need increased cardiovascular performance and tend to have lower HRs.^{30,31} Nonetheless, additional studies are needed to confirm our findings.

Limitations

Our study has several limitations. We defined the sample size using convenience sampling, but a higher number of cases could be better representative of our findings. The analysis of global longitudinal deformation for the 16 LV segments based on Doppler-derived strain could be an option, but it would be less reproducible. However, we showed high intraobserver and interobserver reproducibility for Doppler-derived strain in this study, in addition to the fact that the research objective was to assess the LV region of interest, which is linked to functional status assessment of the coronary artery in this territory. The methodology may have

created selection bias; however, it minimizes the presence of confounding factors.

Conclusion

In this study of patients with normal CFR reached before completion of the DSE, lower HRs found at baseline and at CFR attainment showed a good association with better myocardial contractile performance, according to the change in strain magnitude.

Author contributions

Conception and design of the research and acquisition of data: De Abreu JS, Diógenes TCP, De Abreu MEB; analysis and interpretation of the data: De Abreu JS, Diógenes TCP, De Abreu MEB, Carneiro MM, Farias AGLP; atatistical analysis and critical revision of the manuscript for intellectual content: De Abreu JS, Costa HJM; writing of the manuscript: De Abreu JS, Carneiro MM, Farias AGLP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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