Coronary Flow Velocity Reserve during Dobutamine Stress Echocardiography

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Abstract

Background: A coronary flow velocity reserve (CFVR) ≥ 2 is adequate to infer a favorable prognosis or the absence of significant coronary artery disease.

Objective: To identify parameters which are relevant to obtain CFVR (adequate or inadequate) in the left anterior descending coronary artery (LAD) during dobutamine stress echocardiography (DSE).

Methods: 100 patients referred for detection of myocardial ischemia by DSE were evaluated; they were instructed to discontinue the use of β-blockers 72 hours prior to the test. CFVR was calculated as a ratio of the diastolic peak velocity (cm/s) (DPV) on DSE (DPV-DSE) to baseline DPV at rest (DPV-Rest). In group I, CFVR was < 2 and, in group II, CFVR was ≥ 2. The Fisher’s exact test and Student’s t test were used for the statistical analyses. P values < 0.05 were considered statistically significant.

Results: At rest, the time (in seconds) to obtain Doppler in LAD in groups I and II was not different (53±31 vs. 45±32; p=0.23). During DSE, LAD was recorded in 92 patients. Group I patients were older (65.9±9.3 vs. 61.2±10.8 years; p=0.04), had lower ejection fraction (61±10 vs. 66±6%; p=0.005), higher DPV-Rest (36.81±08 vs. 25.63 ± 06cm/s; p<0.0001) and lower CFVR (1.67 ± 0.24 vs. 2.53 ± 0.57; p<0.0001), but no difference was observed regarding DPV-DSE (61.40±16 vs. 64.23±16cm/s; p=0.42). β-blocker discontinuation was associated with a 4-fold higher chance of a CFVR < 2 (OR = 4; 95% CI [1.171-13.63], p=0.027).

Conclusion: DPV-Rest was the main parameter to determine an adequate CFVR. β-blocker discontinuation was significantly associated with inadequate CFVR. The high feasibility and the time to record the LAD corroborate the use of this methodology.(Arq Bras Cardiol. 2014; 102(2):134-142)

Keywords: Coronary artery disease; Echocardiography, stress / methods; Coronary flow velocity reserve.

Introduction

Pharmacological-stress echocardiography is a safe and accurate noninvasive method for the evaluation of coronary artery disease (CAD)¹-⁴. It has been verified that enhancement of the diastolic component of the flow determined by dobutamine, dipyridamole or adenosine may be used for the calculation of the coronary flow velocity reserve (CFVR)⁵-¹⁹. Measurement of the CFVR by transthoracic echocardiography has already been validated for the assessment of the right and left coronary systems¹⁵,¹⁶,²⁰, and has become an important tool in the functional analysis of the anterior descending coronary artery (LAD). Studies have demonstrated that a CFVR ≥ 2 is adequate and relevant to infer the absence of significant coronary occlusion, and is correlated with a favorable prognosis in the context of the coronary artery analyzed⁷,¹⁰-¹²,¹⁹,²¹-²⁷. Several publications have shown that the authors succeed in recording the LAD flow in approximately 90% of cases; this allows high feasibility of the measurement of CFVR by echocardiography, thus corroborating the use of a safe, validated and reproducible method in the clinical practice⁵-¹¹.

It has been verified that the invasive assessment of CFVR may be influenced by factors such as age, blood pressure, heart rate, left ventricular hypertrophy, degree of coronary impairment, and others²⁸.

Few data are available in the literature regarding the assessment of the functional status of the LAD using dobutamine transthoracic echocardiography. However, regardless of the drug used, the CFVR calculation may be affected for different reasons. Thus, the objective of this study

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was to identify relevant parameters to obtain an adequate (≥ 2) or inadequate CFVR in the LAD during dobutamine stress echocardiography (DSE).

Methods

Study patients

This is a cross-sectional study of 100 patients referred by their physicians for the investigation of myocardial ischemia by means of DSE. The patients had been previously instructed to discontinue the use of betablockers (β-blocker) 72 hours before undergoing the test.

After history taking, the presence of risk factors for CAD and of possible contraindications for DSE was verified. Arterial hypertension was defined as a systolic blood pressure > 140mmHg or diastolic blood pressure > 90mmHg. Diabetes mellitus was confirmed by a fasting plasma glucose > 126mg/dL. Dyslipidemia was considered when total cholesterol > 220mg/dL. The use of antihypertensive drugs, oral hypoglycemic agents, insulin or lipid-lowering drugs was also considered a risk factor for CAD. Patients who had not quit smoking for less than one year prior to the study were considered smokers.

Exclusion criteria were uncontrolled hypertension, unstable angina, congestive heart failure, recent myocardial infarction (MI) (occurring less than one month prior to DSE), significant heart valve disease, prostate disease, or glaucoma with contraindication for the use of atropine, and non-sinus rhythm.

All patients were given information on the risks and objectives of the test, which was only performed after their giving verbal consent.

Dobutamine Stress Echocardiography

The Vivid 7 (GE Healthcare) ultrasound system with second-harmonic imaging and the M4S multifrequency transducer with frequency ranging from 2 to 4MHz were used. The left ventricle (LV) was visualized in the apical views (4 and 2-chamber) and parasternal views (long and short axes) at rest and during the use of dobutamine at the doses of 10 (low dose), 20, 30, up to 40μg/kg/min at 3-min intervals; the rest, low-dose, peak and recovery images were compared in a four-division screen. Atropine could be associated after the second stage at up-titration doses of 0.25mg, up to the maximum cumulative dose of 2mg, with the purpose of terminating the test. DSE was considered terminated when a target heart rate (HR) higher than 85% of the maximum HR (220 – age) was achieved, and/or myocardial ischemia had been determined. Ischemia was considered in the presence of a report of typical angina, new wall motion abnormality, or worsening of a pre-existing wall motion abnormality (except from akinesia to dyskinesia). Tests should be interrupted in the presence of intolerance to medication, hypertensive peak (blood pressure > 230 x 120 mmHg) or cardiac arrhythmia.

The LV was divided into 16 segments. For the wall motion scoring of each segment, the following patterns were observed: normal = 1; hypokinesia = 2; akinesia = 3; or dyskinesia = 4. For the calculation of the segmental wall motion score index (SWMSI), the points obtained were divided by 16 = 4. For the calculation of the segmental wall motion score index (SWMSI), the points obtained were divided by 16 = 4. For the calculation of the segmental wall motion score index (SWMSI), the points obtained were divided by 16 = 4. For the calculation of the segmental wall motion score index (SWMSI), the points obtained were divided by 16 = 4.

Anterior Descending Coronary Artery and Coronary Flow Reserve Velocity Recordings

In the same left lateral position in which DSE was performed, the LAD was recorded at its mid-distal portion with a specific pre-established preset. From the low parasternal long axis recording, with clockwise rotation of the transducer, disappearance of the right ventricle was determined, with visualization of the interventricular sulcus, region in which the LAD imaging would be obtained. Other options were visualization from the position of three modified chambers or two concomitant chambers, with slight angle adjustments or transducer rotation.

Using a small color-Doppler box with Nyquist limit of approximately 20 cm/s, the LAD was identified as a tubular image in which the greatest possible stretching and extension were determined, as well as the lowest angle with the Doppler cursor, whose sample volume measured 2mm. Using pulsed Doppler, the flow assessed was characterized by the biphasic spectrum with diastolic predominance, and antegrade curves above baseline were recorded. Initially, the Doppler velocity scale was limited to 80 cm/s and could be amplified during DSE, thus permitting caption of the subsequent increases in the velocities of the Doppler curves.

In the electrocardiogram-gated Doppler of the LAD, diastolic peak velocities (DPV) were recorded, and three spectral curves, not necessarily continuous, but with good quality and higher velocities were selected at rest and during stress. The CFVR was obtained by dividing DPV (mean of three peaks) found during DSE by the baseline DPV (mean of three peaks) recorded at rest.

Study protocol

After echocardiographic assessment for routine measurements, the LAD was studied. Immediately after placement of the color box in the ultrasound scanner screen, the time spent to obtain the LAD recording by color and pulsed Doppler was counted. Only cases with recordings of Doppler spectral curves obtained in less than 180 seconds would remain in the study. Using the same transducer, visualization of two-dimensional LV imaging was alternated with Doppler of the LAD. Thus, the DSE four-division screen was filled in the different stages, concomitantly with the different DPV measurements until termination of the test. As soon as the test was terminated, the DSE result was defined and the CFVR was calculated. Patients with a CFVR < 2 comprised group I (GI) and those with an adequate CFVR (≥ 2) comprised group II (GII). SWMSI was calculated in a further stage.

Statistical Analysis

The proportion of individuals with an adequate coronary reserve was compared in the different categories of one same independent variable using the Fisher’s exact test. Likewise, the distributions of continuous independent variables, according to the presence or absence of an adequate coronary reserve, were compared using the Student’s t test.

Univariate logistic regression models between independent variables and coronary reserve (adequate and inadequate) were made, and variables with a p value < 0.250 were
included in the multivariate models. The objective of the multivariate analysis was to describe the relationship between β-blocker discontinuation and coronary reserve, adjusted for potential confounders.

**Results**

**Feasibility**

Of the 110 cases initially assessed, 10 were excluded because the time for LAD recording by Doppler exceeded 180 seconds. Consequently, the feasibility for recordings at rest to be obtained within the established time was 91%.

DSEs were performed uneventfully, and DPV could be verified in 92% (92/100) of patients. Of the eight patients not assessed during DSE, the LV twist determined by left bundle branch block impaired visualization in two cases; in the other six, the vigorous heart movements did not allow the recording. Atropine was added in 93% of patients, at a mean dose of 0.68 ± 0.53 mg.

**Clinical Characteristics**

GI was comprised of 32 patients (CFVR < 2) and GII of 60 patients with CFVR ≥ 2 (Figures 1 and 2); patients in GI were older (66±9 vs. 61±11 years; p=0.04).

There was no difference between the groups (p=NS) as regards the distribution by gender, arterial hypertension, dyslipidemia, diabetes, history of CAD, and previous coronary intervention (whether surgical or by catheterization) or MI. Among patients receiving ASA, 48.5% had an inadequate CFVR; among those not receiving ASA, the proportion was 27% (p = 0.044) (Table 1).

All patients were instructed to discontinue β-blocker for 72 hours prior to DSE, and only two of them failed to do so. Both were from GI and their DSE was negative for ischemia. Considering the 22 patients who discontinued the medication, β-blocker was classified as selective in 8 (57%) of the 14 GI patients, whereas in GII, β-blocker was selective in 3 (37.5%) of the 8 cases. Among the 22 patients who discontinued β-blocker, 64% had an inadequate CFVR, whereas among those who did not take or did not discontinue β-blocker, the percentage of inadequate CFVR was 26% (p = 0.002).

There was no difference between the groups as regards their BMI (27.7±6.7 vs. 27.5±3.8 kg/m²; p = 0.87). Among the 92 patients, 40 (43.5%) were overweight (BMI≥ 25 kg/m²), 22 (24.5%) were obese (BMI ≥ 30 kg/m²) and one had morbid obesity (BMI ≥ 40 kg/m²)10,33.

**Echocardiographic Recordings and Hemodynamic Data**

LV ejection fraction in GI and GII were different (61±10 vs. 65.8±5.7%; p = 0.005). There were no differences (p = NS) between the groups regarding LV mass, blood pressure (systolic and diastolic) at rest and in DSE, or the double product (Table 2). In GII, higher HR were achieved during DSE (148±12 vs. 141±20bpm; p = 0.04); however, in only 20% (18 cases) of the study patients the DSE was terminated with maximum HR. Among patients who achieved maximum HR, 66.7% showed CFVR < 2, whereas CFVR was inadequate in 27% of those who did not achieve maximum HR (p = 0.002).

Five DSEs were inconclusive (all in GI); six were positive for myocardial ischemia, three in each group; and only in one case the anterior wall was affected (GI). SWMSI was not different between the groups (1.05±0.2 vs. 1.02±0.7; p = 0.24) during DSE.

**Doppler recording of the LAD**

The mean time to obtain Doppler spectrum of the LAD in both groups was shorter than one minute, with no differences between them (p = 0.23). Likewise, the mean HR at the moment the DPVs were obtained, whether at baseline or during DSE, were not significantly different between the groups either. In 33 (55%) of GII patients, an adequate CFVR was obtained before achieving the established target HR.

The baseline DPV in GI was higher than in GII (36.8 ± 8.4 vs. 25.6±5.7 cm/s; p< 0.0001). However, there was no difference between DPVs obtained during DSE (61.4±16.6 vs. 64.2±15.9 cm/s; p=0.42), thus resulting in CFVR of GI < GII (1.66±0.24 vs. 2.53±5.7; p< 0.0001) (Table 3).

**Multivariate analysis of parameters**

In the multivariate model, the logistic regression analysis for CFVR < 2 showed significance for age and for β-blocker discontinuation (Table 4). The multivariate model was adjusted for potential confounders, and patients who had discontinued β-blocker had a four-fold higher chance of showing an inadequate CFVR (Table 5).

**Discussion**

In the daily practice, it is important to consider the time spent to perform the procedures. For this reason, we limited the time to obtain Doppler recordings (color and pulsed) of the LAD at rest at 180 seconds (period of one DSE stage), with a significant success rate (91%). During DSE, the high performance (92%) of Doppler recording of the LAD was maintained, and the feasibility rates were comparable to those of other studies using dobutamine or vasodilators.

In the present study, we sought to verify clinical, echocardiographic or hemodynamic parameters associated with the CFVR cut-off point established as adequate. Patient inclusion was not limited by the presence of cardiovascular risk factors, and these factors were not significantly associated with adequate or inadequate CFVR. GI patients were older and had a lower mean ejection fraction, factors that may be related to a low CFVR.

In the univariate analysis, the use of ASA was associated with inadequate CFVR. However, in the multivariate analysis, this was not demonstrated (Table 4).

β-blockers decrease the possibility of ischemia by reducing the cardiac work. Thus, discontinuation of these drugs promotes a higher HR, and this could increase the probability of a more frequent occurrence of DSE with achieved target HR or consistent with myocardial ischemia. Previous findings suggest that non-selective β-blocker increases coronary vascular resistance34. On
the other hand, the use of selective β-blocker increases myocardial perfusion and improves coronary flow reserve, thus reducing the possibility of ischemia. In methodologies of studies related to stress echocardiography, some authors do not interfere in the use of β-blocker, whereas others discontinue the drug for 24 to 48 hours prior to DSE. In our study, patients were instructed to discontinue the drug for 72-hour with the purpose of reducing the occurrence of inconclusive DSE. However, the findings showed an additional importance regarding the effect of this drug, since a significant association between β-blocker discontinuation and the occurrence of inadequate CFVR was observed (Table 1). This finding could be related to the loss of a protective effect of the β-blocker, although we cannot rule out that this result had been related to peculiar characteristics of the study sample.

Figure 1 - Diastolic peak velocity (DPV), coronary flow velocity reserve (CFVR) and correlated heart rate (HR). Group I: DPV = 45 cm/s and HR = 65 bpm at rest (A) with DPV = 77 cm/s and HR = 139 bpm during stress (B), determining CFVR = 1.71 after achieving the target HR (138). Group II: DPV = 34 cm/s and HR = 90 bpm at rest (C) with DPV = 89 cm/s and HR = 137 bpm during stress (D), determining CFVR = 2.61 after achieving the target HR (131).

Figure 2 - CFVR = 3 was obtained early (HR = 118 bpm) in relation to the target HR (140 bpm).
Table 1 - Characteristics of a sample (N=92) of patients undergoing dobutamine stress echocardiography, according to the category of coronary flow velocity reserve (CFVR)

| Clinical characteristics | Total | Group I (CFVR < 2) | Group II (CFVR ≥ 2) | p       |
|--------------------------|-------|-------------------|---------------------|---------|
|                          | N (%  | N (%)             | N (%)               |         |
| Male                     | 53    | 14 (45)           | 39 (65)             | 0.07    |
| Female                   | 39    | 18 (46)           | 21 (54)             |         |
| Hypertension             |       |                   |                     |         |
| - Absent                 | 26    | 6 (23)            | 20 (77)             | 0.155   |
| - Present                | 66    | 26 (39.4)         | 40 (60.6)           |         |
| Dyslipidemia             |       |                   |                     |         |
| - Absent                 | 33    | 12 (36.4)         | 21 (63.6)           | 0.823   |
| - Present                | 59    | 20 (34)           | 39 (66)             |         |
| Diabetes                 |       |                   |                     |         |
| - Absent                 | 75    | 26 (34.7)         | 49 (65.3)           | 1.000   |
| - Present                | 17    | 6 (35.3)          | 11 (64.7)           |         |
| Use of ASA               |       |                   |                     |         |
| - No                     | 59    | 16 (27)           | 43 (73)             | 0.044   |
| - Yes                    | 33    | 16 (48.5)         | 17 (51.5)           |         |
| Use of Statin            |       |                   |                     |         |
| - No                     | 49    | 17 (34.7)         | 32 (65.3)           | 1.000   |
| - Yes                    | 43    | 15 (35)           | 28 (65)             |         |
| Use of ACE or ARA Inhibitor |     |                   |                     |         |
| - No                     | 45    | 16 (35.6)         | 29 (64.4)           | 1.000   |
| - Yes                    | 47    | 16 (34)           | 31 (66)             |         |
| Use of Nitrate           |       |                   |                     |         |
| - No                     | 86    | 29 (34)           | 57 (66)             | 0.416   |
| - Yes                    | 6     | 3 (50)            | 3 (50)              |         |
| Betablocker               |       |                   |                     |         |
| - Did not take or did not discontinue | 70 | 18 (26) | 52 (74) | 0.002 |
| - Discontinued           | 22    | 14 (64)           | 8 (36)              |         |
| History of CAD           |       |                   |                     |         |
| - Absent                 | 67    | 20 (30)           | 47 (70)             | 0.140   |
| - Present                | 25    | 12 (48)           | 13 (52)             |         |
| Previous CI              |       |                   |                     |         |
| - Absent                 | 72    | 24 (33)           | 48 (67)             | 0.603   |
| - Present                | 20    | 8 (40)            | 12 (60)             |         |
| Previous MI              |       |                   |                     |         |
| - Absent                 | 87    | 31 (35.6)         | 56 (64.4)           | 0.655   |
| - Present                | 5     | 1 (20)            | 4 (80)              |         |

ASA: Acetyl salicylic acid; ACE: Angiotensin converting enzyme; ARA: Angiotensin receptor antagonist; CAD: Coronary artery disease; CI: Coronary intervention; MI: Myocardial infarction.

In the multivariate model, the statistical analysis showed significance for age and β-blocker discontinuation (Tables 4 and 5). During this time window of β-blocker discontinuation, the patients had a four-fold higher chance of presenting inadequate CFVR. This is an interesting observation and suggests that we should be aware of the selectivity of the β-blocker in use and of the doses administered (characteristics that were not recorded for all patients), and question whether there is a better time...
interval for β-blocker discontinuation when evaluating CFVR by dobutamine transthoracic echocardiography.

In Meimon et al study⁷, the CFVR obtained in the general population with adenosine (2.5) and dobutamine (2.4) was similar to that found in group II of the present study (2.53). Meimon et al⁷ study patients with wall motion abnormalities consistent with ischemia on DSE showed low CFVR with adenosine (1.5) and dobutamine (1.6), values close to those found in our group with low CFVR (1.67). However, we did not find correlation with wall motion abnormality. We point out that 91% (43/47) of Meimon et al study patients⁷ had known CAD. It is possible that, in addition to different populations, the time of β-blocker discontinuation, dose and selectivity, as well as the HR achieved may have determined different results in the two studies.

CFVR can increase progressively with the increase in HR in patients without wall motion abnormality consistent with ischemia during DSE⁷ or those at a low risk for CAD with DSE without ischemic response¹². Also, increases in CFVR can be limited or even reduced in the presence of wall motion abnormality consistent with ischemia of the anterior wall⁵-⁸. Although GI had lower CFVR, the recordings did not show a reduction in DPV values during DSE.

The mean DPV obtained during DSE in the two groups of our study were not different, and we should point out that the mean HR at the moment of the DPV recordings did not differ either. This finding is relevant since, in principle, we know that DPVs increase concomitantly with the increase in HR. The mean HR recorded at the end of DSE were higher, and this suggests a difficulty to obtain Doppler of the LAD in periods closer to the maximum HR obtained.

Table 2 - Echocardiographic and hemodynamic recordings, according to categories (Groups I and II) of coronary flow velocity reserve

| Parameters                | Group I (N = 32) | Group II (N = 60) | p    |
|---------------------------|------------------|-------------------|------|
|                          | Mean             | Standard Deviation | Mean | Standard Deviation |      |
| Left ventricle            |                  |                   |      |                    |      |
| Ejection fraction (%)     | 61               | 1.8               | 65.8 | 0.7               | 0.005|
| Mass (gr)                 | 250.5            | 17.5              | 232.4| 8.9               | 0.30 |
| Mass / BS (g/m²)          | 142.5            | 9.2               | 128.5| 4.7               | 0.13 |
| Heart rate (bpm)          |                  |                   |      |                    |      |
| Baseline                  | 72               | 2.3               | 67   | 1.4               | 0.058|
| During DSE                | 141              | 3.5               | 148  | 1.5               | 0.04 |
| Blood pressure (mmHg)     |                  |                   |      |                    |      |
| Systolic (Baseline)       | 131              | 3.3               | 126  | 1.8               | 0.17 |
| Systolic (DSE)            | 151              | 3.1               | 152  | 2.1               | 0.08 |
| Diastolic (Baseline)      | 78               | 1.3               | 78   | 0.8               | 0.85 |
| Diastolic (DSE)           | 83               | 1.7               | 80   | 1.2               | 0.25 |
| Double Product (mmHg x bpm) during DSE | 21263 | 685 | 22423 | 380 | 0.11 |

BS: Body surface; DSE: Dobutamine stress echocardiography; Double product: systolic blood pressure x heart rate.

Table 3 - Measurements obtained during Doppler in the anterior descending coronary artery

| Parameters                      | GI        | Standard Deviation | GI        | Standard Deviation | p     |
|---------------------------------|-----------|--------------------|-----------|--------------------|-------|
| Time (seconds) to obtain Doppler of the LAD | 53        | 5.5                | 45        | 4.1                | 0.23  |
| HR at recording of baseline DPV |           |                    |           |                    |       |
| Basal (bpm)                     | 72        | 2.3                | 67        | 1.4                | 0.058 |
| During DSE (bpm)                | 123       | 5.0                | 119       | 2.7                | 0.47  |
| DPV (cm/s) Baseline             | 36.8      | 0.014              | 25.6      | 0.07               | < 0.0001|
| DPV (cm/s) on DSE               | 61.4      | 0.029              | 64.2      | 0.020              | 0.42  |
| CFVR (DPV on DSE + baseline DPV)| 1.67      | 0.042              | 2.53      | 0.073              | < 0.0001|

LAD: Left anterior descending coronary artery; HR: heart rate, DPV: Diastolic peak velocity; DSE: Dobutamine stress echocardiography; CFVR: Coronary flow velocity reserve.
### Table 4 - Multivariate logistic regression analysis for CFVR < 2

| Parameters   | OR       | p       | CI 95%       |
|--------------|----------|---------|--------------|
| Age          | 1.053882 | 0.037   | 1.003145     |
| Ejection F.  | 0.9426074| 0.118   | 0.8644104    |
| LV Mass /BS  | 1.004491 | 0.517   | 0.9909688    |
| Betablocker   | 3.997332 | 0.027   | 1.17166      |
| ASA          | 1.460583 | 0.598   | 0.3569187    |
| SH           | 1.07366  | 0.913   | 0.3009711    |
| CAD          | 0.778762 | 0.747   | 0.1709659    |

OR: Odds ratio; CI: Confidence interval; LL: Lower limit; UL: Upper limit; LV Mass/BS: left ventricular mass indexed for body surface; ASA: acetyl salicylic acid; SH: systemic hypertension; CAD: coronary artery disease.

### Table 5 - Multivariate models of the relationship between variables and coronary flow velocity reserve as measured by dobutamine stress echocardiography

| Multivariate model | OR       | Standard Deviation | 95% CI OR | p       |
|--------------------|----------|--------------------|-----------|---------|
| Betablocker        | 5.05     | 2.6                | 1.62-14.03| 0.002   |
| Betablocker        | 3.9      | 2.5                | 1.17-13.64| 0.027   |
| Betablocker        | 4.17     | 2.4                | 1.35-12.82| 0.013   |

1Non-adjusted model. 2Complete model, adjusted for age, ejection fraction, left ventricular mass/body surface, use of ASA, arterial hypertension, coronary artery disease. €Model adjusted for age and ejection fraction. Other variables, when retrieved from the complete model, modified the OR by less than 10%.

It was very important to have found that GII patients showed lower DPVs at rest; however, DPVs were similar between the two groups during DSE, thus making the value obtained at rest the determinant factor to result in an adequate CFVR.

### Limitations

The learning curve was an important phase to be addressed before the beginning of this study, since LAD recording during DSE is very arduous.

Although the number of study patients was satisfactory in comparison to those of other studies, a larger sample could maybe provide more information regarding the parameters assessed. Additionally, the posology of the β-blocker used was not recorded. Like in other studies, the patients did not undergo coronary angiography, and this makes it impossible to know whether CFVR, be it adequate or not, could be related to impairment of the stenotic large epicardial coronary arteries and/or of the microcirculation. The lower number of DSEs at a maximum HR level may have compromised the accuracy of the assessment of ischemia for wall motion abnormality, which could have contributed to the occurrence of false-negative DSEs. Another important limitation was that the inter- and intraobserver variation for DPV measurements was not calculated. A possibility that cannot be ruled out, although unlikely, is that recordings of a diagonal branch had been misinterpreted as those of LAD.

Like in other studies, ours assessed only LAD. We calculated the coronary reserve by means of velocity, not flow; however, this becomes less relevant since the analysis of flow velocity may represent the functional status of the vessel, and CFVR calculation is the result of a ratio.

### Clinical Applications

The literature shows that the finding of an adequate CFVR is of great diagnostic or prognostic value, and represents a relevant complementary information for clinical, interventionist or surgical decision-making.

Considering the territory supplied by the LAD, it is important to notice that, even in cases of inconclusive DSEs by the criteria of HR achieved, it is possible to obtain a CFVR ≥ 2 and infer that perfusion is satisfactory in that region. Likewise, obtaining an adequate CFVR, concomitantly with normal segmental anterior wall motion by the end of a terminated DSE, may contribute to the echocardiographic diagnosis of absence of ischemia in this myocardial segment, especially in tests in which the maximum HR is not achieved.

The availability, low cost, reproducibility and accuracy of this method, make it an important tool for the functional assessment of the coronary artery. In this study, we evaluated parameters that could or not be related to an adequate CFVR. In this context, conditions such as DPV at rest, age, ejection fraction, and the use of medication may be significantly associated.

### Conclusions

The DPV obtained at rest is an important parameter in the determination of an adequate CFVR. β-blocker discontinuation was significantly associated with an inadequate CFVR. The high feasibility and short time interval spent for recording the LAD corroborates the application of this method in the daily practice.
Author contributions
Conception and design of the research: Abreu JS; Acquisition of data: Abreu JS, Diógenes TCP, Gomes Neto PS; Analysis and interpretation of the data: Abreu JS, Lima JWO, Siqueira JM, Paes Júnior JN; Critical revision of the manuscript for intellectual content: Abreu JS, Lima JWO.

Potential Conflict of Interest
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