Pressure-Volume Relationship By Pharmacological Stress Cardiovascular Magnetic Resonance

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Original Article
Abstract

Background. The variation between rest and peak stress end-systolic pressure-volume relation (ΔESPVR) is an index of myocardial contractility, easily obtained during routine stress echocardiography and never tested during dipyridamole stress-cardiac magnetic resonance (CMR). We assessed the ΔESPVR index in patients with known/suspected coronary artery disease (CAD) who underwent dipyridamole stress-CMR.

Methods. One-hundred consecutive patients (24 females, 63.76±10.17 years) were considered. ESPVR index was evaluated at rest and stress from raw measurement of systolic arterial pressure and end-systolic volume by biplane Simpson's method.

Results. The ΔESPVR index showed a good inter-operator reproducibility. Mean ΔESPVR index was 0.48±1.45 mmHg/mL/m2. ΔESPVR index was significantly lower in males than in females.

ΔESPVR index was not correlated to rest left ventricular end-diastolic volume index or ejection fraction. Forty-six of 85 patients had myocardial fibrosis detected by the late gadolinium enhancement technique and they showed significantly lower ΔESPVR values. An abnormal stress CMR was found in 25 patients and they showed significantly lower ΔESPVR values.

During a mean follow-up of 56.34±30.04 months, 24 cardiovascular events occurred. At receiver-operating characteristic curve analysis, a ΔESPVR<0.02 mmHg/mL/m2 predicted the presence of future cardiac events with a sensitivity of 0.79 and a specificity of 0.68.

Conclusions. The noninvasive assessment of the ΔESPVR index during a dipyridamole stress-CMR exam is feasible and reproducible. The ΔESPVR index was independent from rest LV dimensions and function and can be used for a comparative assessment of patients with different diseases. ΔESPVR by CMR can be a useful and simple marker for additional prognostic stratification.

Introduction

Cardiac contractility is the intrinsic capability of heart muscle to generate force and to shorten, ideally independently of changes in heart rate, preload or afterload. Several noninvasive methods have been explored to quantify myocardial contractility and contractile reserve [1]. The end-systolic pressure-volume ratio (ESPVR), defined as the ratio between the systolic pressure and the left ventricular (LV) end-systolic volume indexed for body surface area [2], assessed at rest and during stress, relies on the fact that a positive inotropic stimulation should be accompanied by higher end-systolic pressures with smaller end-systolic volumes. This index has become the most reliable noninvasive measure of contractility, being almost insensitive to changes in preload and afterload [3]. The ESPVR assessment was introduced into the nuclear medicine [2] and the echo laboratories many years ago [4, 5]. Due to the greater availability and lower cost, better spatial and temporal resolutions, and absence of biohazards for the patient and the
physician [6], echocardiography has become the primary method for determining ESPVR. The $\Delta$ESPVR, calculated as the variation between rest and peak stress ESPVR, was subsequently introduced in the stress-echocardiography as a measure of the heart rate-dependent changes in contractility [4] and it showed significant advantages over the rest or the peak ESPVR value. The $\Delta$ESPVR is more strongly linked with peak hemodynamic response and stress systolic function [1]. Moreover, it is a more independent measure of true contractile reserve, being unrelated to rest function [1] and to the size of the ventricle [7]. Different $\Delta$ESPVR cut-offs for the prediction of cardiovascular events were described, depending on the type of stress (exercise, dobutamine or dipyridamole), type of population, and considered end-points [5, 8, 3, 9–11].

In the last decade, stress-cardiac magnetic resonance (CMR) imaging has become a well-established technique for the diagnosis and prognostic stratification of patients with acute and chronic ischemic heart disease [12]. Compared to stress-echocardiography, stress-CMR can provide high-quality images for the visualization of global and regional left ventricular wall motion and highly accurate and reproducible measures of both ventricles [13]. Finally, CMR can provide additional information, such as the detection of perfusion defects and of myocardial fibrosis. Perfusion abnormalities are expected to occur before the regional wall motion abnormalities in the ischemic cascade. Although assessment of myocardial perfusion by stress-echocardiography is technically possible, the methodology is challenging, relatively complicated and lacks of standardization [14]. Several studies demonstrated the additional value of first-pass myocardial perfusion imaging to wall motion assessments during stress-CMR to improve sensitivity for the diagnosis of significant coronary artery disease (CAD) [15, 16]. Moreover, CMR by late gadolinium enhancement (LGE) is the noninvasive reference standard for replacement fibrosis detection, with significant diagnostic and prognostic implications. Pharmacological stress-CMR can be performed using either inotropic (dobutamine) or vasodilator (adenosine or dipyridamole) stimuli [17] and recent studies have demonstrated the feasibility of exercise stress test, acquiring images immediately following maximal treadmill exercise or with in-scanner cycle ergometers [18, 19]. Nevertheless, currently vasodilator stress agents remain the mainstay of stress-CMR due to safety issues [20].

The estimation of the $\Delta$ESPVR by CMR is appealing but only few attempts have been made, based on the invasive measurement of blood pressures [21] and assessment of volumes at rest and during bicycle exercise in healthy endurance athletes in comparison to patients with dilated cardiomyopathy [22]. No data are available in literature evaluating the $\Delta$ESPVR by dipyridamole stress-CMR.

We assessed the feasibility of a noninvasive estimation of $\Delta$ESPVR during dipyridamole stress-CMR in patients with known or suspected coronary artery disease (CAD). Moreover, we evaluated the dependence of the $\Delta$ESPVR on LV size and function, its association with macroscopic myocardial fibrosis, and its prognostic implications.

**Materials And Methods**

**Study population**
We enrolled 100 consecutive patients (24 females, mean age 63.76±10.17 years) with known or suspected CAD who underwent dipyridamole stress-CMR in a high volume CMR Laboratory between November 2004 and December 2016, based on the clinical indication [23].

Exclusion criteria were unstable angina, heart failure, known infiltrative or hypertrophic cardiomyopathy, hemodynamic instability, absolute contraindication to CMR and to dipyridamole use, execution of an early revascularization (within 60 days after stress CMR), and a follow-up duration shorter than 6 months.

The electronic medical records of all patients were retrospectively reviewed for demographic data, presence of cardiovascular risk factors and cardiovascular therapy.

Our study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent at the time of the CMR.

**CMR**

CMR was performed using a 1.5 T MR scanner (GE Excite HD). An eight-element cardiac phased-array receiver surface coil with breath-holding in end-expiration and ECG-gating was used for signal reception.

Patients were asked to refrain from smoking, caffeine, and theophylline for 24 hours, to suspend beta-blockers for 48 hours, and to maintain fasting for 4 hours. Steady-state free precession (SSFP) cine images were acquired at rest in sequential 8 mm short axis (no interslice gap) and 2- and 4-chamber views of the left ventricle.

Vasodilatation was induced with dipyridamole injected at 0.84 mg/kg over 5 minutes. At the end of dipyridamole infusion, 0.1 mmol/kg of Gadolinium (0.5 mol/l) was injected intravenously at 4 mL/s followed by saline solution with concomitant acquisition of three short-axis views of the left ventricle with first-pass perfusion technique using saturation-prepared T1-weighted fast gradient-echo sequence.

Steady-state free precession cine images were then acquired at stress in 4- and 2-chamber views and in basal, medium and apical short-axis views (3 slices per heart beat) with the same geometry used at rest, according to the standard stress-CMR protocols [24]. Aminophylline was intravenously injected to null the effect of dipyridamole at the end of the stress test. About after ten minutes when cardiac frequency and blood pressure returned to the basal state, 0.1 mmol/kg of Gadolinium was injected intravenously at 4 ml/s followed by saline solution with concomitant acquisition of three short-axis views of the left ventricle with first-pass perfusion technique using saturation-prepared T1-weighted fast gradient-echo sequence. Eight minutes after contrast injection, breath-hold contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo sequence was acquired with the same prescriptions for cine images to detect LGE. The inversion time was individually adjusted to null normal myocardium.

**Image analysis**

CMR images were blindly analyzed using certified software (cvi42, Circle CVI, Calgary, Alberta, Canada).
LV end-diastolic and end-systolic volumes (EDV, ESV) were obtained at rest and at peak of stress from apical vertical long-axis view and horizontal long-axis view using the biplane Simpson’s method (Figure 1). The LV ejection fraction (EF) was calculated according to the formula EF = (EDV - ESV)/EDV 100%. EDV and ESV were normalized for the body surface area (EDVI and ESVI).

LV EDV and ESV were calculated at rest also by cine short-axis slices using the standard method [25].

The 17-segment model of the American Heart Association/American College of Cardiology was applied [26] for the analysis of wall motion, perfusion and myocardial fibrosis.

Wall motion at rest and after dipyridamole was analyzed by classifying each myocardial segment as normal, hypokinetic, akinetic or diskinetic. Ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality. Perfusion defect was evaluated at rest and after stress and was defined as persistent delay of enhancement during first pass of the contrast agent for >3 heartbeats at maximum signal intensity in the cavity of the left ventricle.

The LGE was evaluated visually using a two-point scale (enhancement absent or present). Enhancement was considered present whenever it was visualized in two different views. The number of myocardial segments showing LGE was assessed.

**Pressure assessment**

Systolic blood pressures at rest and stress were recorded in the right arm by using a MRI-compatible sphygmomanometer immediately before the acquisition of cine images. The end-systolic pressure was obtained as LV end-systolic pressure=0.9*systolic blood pressure.

**End-systolic pressure-volume assessment**

The ESPVR index (mmHg/mL/m2) was obtained as the ratio of the end-systolic pressure to the LVESVI calculated from the long axis views. The ESPVR index was determined at rest and at peak stress. The ΔESPVR index was calculated as the difference between rest and peak stress ESPVR [5].

**Follow-up**

Patients follow-up was performed by phone interview or review of informatic medical records by researchers unaware of the patients’ CMR results.

The following end-points were considered: non-fatal myocardial infarction, revascularization defined as elective procedure 60 days after CMR, hospitalisation for unstable angina or heart failure, ventricular arrhythmias, and cardiac death.

In cases of multiple events in a given patient, the first event was considered.

**Statistical analysis**
All data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc for Windows version 7.2.1.0 (MedCalc Software, Mariakerke, Belgium) statistical packages.

Continuous variables were described as mean±standard deviation (SD). Categorical variables were expressed as frequencies and percentages.

The Kolomogorov-Smirnov test showed a non-normal distribution for rest and stress ESPVR and ΔESPVR values. Comparisons between groups were made by the Wilcoxon rank sum test and correlation analysis was performed using the Spearman's test.

A receiver-operating characteristic (ROC) analysis was used to obtain the best prognostic predictor for ΔESPVR.

A 2-tailed P<0.05 was considered statistically significant.

Reproducibility analysis

To evaluate the inter-observer variability, images from 20 patients were presented in random order to another operator. A paired Wilcoxon signed rank test was applied to detect significant differences between the two datasets and the intraclass correlation coefficient (ICC) was obtained from a two-way random effects model with measures of absolute agreement. An ICC≥0.75 was considered excellent. The agreement between measurements was evaluated through the use of Bland-Altman (BA) analysis by calculating the bias (mean difference) and the 95% limits of agreement (mean±1.96 SDs).

Results

Patients characteristics

By selection, technically adequate images were obtained in all patients at rest and during stress, and no test was interrupted because of major complications.

Table 1 shows the main clinical and CMR findings of the study population. Mean ESPVR index at rest and peak stress was, respectively, 4.84±2.47 mmHg/mL/m2 and 5.33±3.16 mmHg/mL/m2 and mean ΔESPVR index was 0.48±1.45 mmHg/mL/m2.

Inter-operator reproducibility

In 20 randomly selected patients no significant difference was detected between the ΔESPVR values calculated by the two operators (0.62±1.63 mmHg/mL/m2 vs 0.75±1.62 mmHg/mL/m2; P=0.478). The ICC was excellent (0.959; 95%CI=0.899-0.984). The BA analysis showed a bias of -0.11 while BA limits were -1.34 and 1.11.

Correlates of ΔESPVR
Rest LV volumes calculated using the biplane Simpson's method were comparable to volumes obtained from short axis images using standard method (EDVI: mean difference 1.78±17.89 ml/m2 P=0.588 and ESVI: mean difference -1.80±8.49 ml/m2 P=0.344).

ΔESPVR index was not associated to age (R=-0.107; P=0.290) but it was significantly lower in males than in females (0.25±1.24 mmHg/mL/m2 vs 1.22±1.79 mmHg/mL/m2; P=0.017).

Patients without and with diabetes showed comparable values of ΔESPVR (0.56±1.58 mmHg/mL/m2 vs 0.26±0.99 mmHg/mL/m2; P=0.497).

A significant inverse relationship between ESPVR index and LVEDVI was present at rest (R=-0.795; P<0.0001) and peak stress (R=-0.779; P<0.0001). ΔESPVR index was not correlated to rest LVEDVI (R=-0.120; P=0.233) while it showed a weak correlation with stress LVEDVI (R=-0.240; P=0.016).

A significant positive relationship between ESPVR index and LVEF was present at rest (R=0.841; P<0.0001) and stress (R=0.882; P<0.0001). ΔESPVR index was not correlated to rest LVEF (R=0.193; P=0.055) but it was significantly correlated with stress LVEF (R=0.557; P<0.0001).

LGE sequences were acquired in 85 patients. Forty-six (54.1%) patients showed myocardial fibrosis: 27 with an ischemic pattern (11 transmural, 10 subendocardial, and 6 transmural and subendocardial), 15 with a non-ischemic pattern (11 mid-wall, 3 epicardial, and 1 both mid-wall and epicardial), and 4 with a mixed pattern. Patients with myocardial fibrosis showed a significantly lower ΔESPVR index compared to patients without myocardial fibrosis (0.19±1.08 mmHg/mL/m2 vs 0.82±1.73 mmHg/mL/m2; P=0.031) (Figure 2A). Mean number of segments with myocardial fibrosis was 3.96±2.43 and a significant correlation was detected between the ΔESPVR index and the number of segments with myocardial fibrosis (R=-0.519; P<0.0001).

An abnormal stress-CMR was found in 25 (25.0%) patients; 19 patients had a reversible stress perfusion defect in at least one myocardial segment and 6 a reversible stress perfusion defect plus worsening of stress wall motion in comparison with rest. ΔESPVR index was significantly lower in patients with abnormal stress-CMR than in patients with normal stress-CMR (0.21±1.57 mmHg/mL/m2 vs 0.57±1.40 mmHg/mL/m2; P=0.035) (Figure 2B).

**Follow-up data and ROC analysis**

Mean follow-up time was 56.34±30.04 months (median=52.88 months).

Cardiac events were recorded in 24 (24%) patients: 3 cardiac deaths, 11 revascularizations after unstable angina (N=10) or myocardial infarction (N=1), 1 ventricular arrhythmia, and 9 hospitalisations for heart failure (N=2) or unstable angina (N=7).

Mean time from the CMR scan to the development of a cardiac event was 36.19±28.21 months (range 3-125 months). Mean age at the appearance of the cardiac events was 68.25±10.21 years (range 49-85
Patients with events showed a significant lower ΔESPVR index (-0.14±0.91 mmHg/mL/m² vs 0.68±1.53 mmHg/mL/m²; P=0.002) (Figure 3A).

At ROC curve analysis, ΔESPVR index<0.02 mmHg/mL/m² predicted the presence of future cardiac events with a sensitivity of 0.79 and a specificity of 0.68 (P=0.0004). The area under the curve was 0.71 (95% Confidence interval: 0.61-0.79) (Figure 3B).

If only the 75 patients with a normal stress CMR exam were considered, ΔESPVR index<0.02 mmHg/mL/m² remained the best value to predict future events, with a sensitivity of 0.69 and a specificity of 0.73.

**Discussion**

We showed for the first time that a noninvasive and reproducible estimation of ΔESPVR can be easily done during dipyridamole stress-CMR. Mean ΔESPVR index in our population of patients with known or suspected CAD was 0.48±1.45 mmHg/mL/m². Although it is hazardous to compare different techniques and study populations, by dipyridamole stress-echocardiography Bombardini et al found a mean value of 2.75±2.17 mmHg/mL/m² in 33 subjects with a low pretest probability of coronary artery disease and of -0.10±2.39 mmHg/mL/m² in 140 patients with CAD, diagnosed in presence of history of myocardial infarction or coronary revascularization and/or the presence of ≥1 angiographically documented coronary stenosis > 50% [7].

We found out that ΔESPVR index was associated to gender, being significantly higher in females. To our knowledge no previous study has attempted to explore the gender differences in the ΔESPVR values. Jellis et al found a comparable percentage of males and females with a reduced ΔESPVR index after exercise [1], but no data are available in literature about direct comparisons of the mean values for ΔESPVR index by gender. Although it is insidious to translate results from experimental studies, our data find echo in the work of Capasso et al, aimed at defining the contractile properties of left ventricular papillary muscles in the rat [27]. The authors found out that, although there was no difference in peak isometric tension developed, the males took longer to develop maximal force and relaxed more slowly. In addition, an increase in external calcium did not affect these gender-specific contractile properties.

Rest and peak stress end-systolic pressure-volume ratios were dependent on chamber size, resulting lower in larger ventricles. Conversely, the rest LVEDVI did not affect the ΔESPVR index. These findings are in agreement with a recent study based on stress echocardiography [7] and emphasize that the ΔESPVR index represents an optimal index for comparative assessments even in patients with pathological left ventricular dilatation, without the need of size normalization. Moreover, we detected a significant positive correlation between ΔESPVR index and stress systolic function, that is a central clinical determinant of LV contractility and contractile reserve [1].
A reduced $\Delta$ESPVR index was associated with the presence of macroscopic myocardial fibrosis, detected by the LGE technique. Myocardial fibrosis is a complex process resulting in the excessive accumulation of the extracellular matrix proteins by cardiac fibroblasts converted to their activated form, often known as myofibroblasts [28]. Fibrotic extracellular matrix increases the stiffness and decreases the compliance of the tissue, negatively affecting both contraction and relaxation of the heart and leading to a progressive decrease in contractility [29-31]. In the subgroup of LGE-positive patients, a negative correlation was detected between the $\Delta$ESPVR index and the number of segments with myocardial fibrosis, suggesting that the contractility worsens as the extent of macroscopic myocardial fibrosis increases.

Patients with an abnormal stress CMR showed a significant lower $\Delta$ESPVR index than patients with a normal stress CMR. However, there was an overlap between the two groups. This finding suggests that a depressed $\Delta$ESPVR index can be a marker of initial and latent LV dysfunction in patients with minor forms of anatomically significant CAD which are unable to give absolute subendocardial under perfusion necessary to induce true regional ischemia. In fact, it has been shown that in patients with negative stress-echocardiography by standard wall motion criteria, a $\Delta$ESPVR index<1.5 mmHg/ml/m2, as determined by ROC analysis cut-off, was an independent predictor of total events [3].

A lower $\Delta$ESPVR index was associated with the development of cardiovascular events. With a ROC analysis, a $\Delta$ESPVR index <0.02 mmHg/mL/m2 predicted future events with good sensitivity and specificity. Further dipyridamole stress-CMR studies are needed to confirm this observation in order to include definitively this parameter in the clinical practice.

**Limitations**

1) The study population was not so large because in our Laboratory we used also other stress-agents, such as dobutamine and adenosine. Moreover, we were used to scan patients in all field of cardiology, not only patients with suspicion of ischemic disease.

2) As only non-invasive measurements of blood pressure were available, the systolic cuff pressure was used as a surrogate for end-systolic pressure, introducing an approximation.

3) We assumed that $V_0$ (zero-volume intercept of the end-systolic pressure–volume relationship) was negligible. The calculation of $V_0$ requires the use of invasively derived pressure–volume loops, which was not possible in this noninvasive study. However, previous studies reported that $V_0$ remains unaltered during exercise or changes in loading conditions [32], making the LVESPVR index a valid approximation of end-systolic elastance [33].

4) Short axis slices are used in non-stress-CMR for the assessment of LV volumes and function and represent the gold standard [25]. However, in the stress-CMR, the evaluation of function parameters during stress can be performed using the long axis views, in order to reduce the total scan time for safety reasons [24]. Anyway, both approaches were significantly correlated in our study population and it has
been shown that, when compared to an ex vivo standard, both, short axis and long axis techniques are highly accurate for the quantification of left ventricular volumes and mass [34].

5) The obtained cut-off can be applied only for $\Delta$ESPVR indexes obtained during a dipyridamole stress-CMR exam, since it is entirely likely that prognostically meaningful cut-offs for this index are stress-specific [35].

**Conclusions**

The noninvasive assessment of the $\Delta$ESPVR index during a dipyridamole stress-CMR exam is feasible, reproducible, free and it does not affect the imaging time. $\Delta$ESPVR index was independent from rest chamber size, while it was reduced in presence of abnormal stress-CMR and myocardial fibrosis. In patients with known or suspected CAD who undergo dipyridamole stress-CMR $\Delta$ESPVR index can provide a prognostic stratification for relevant cardiac events with an optimal cut-off of 0.02 mmHg/mL/m².

**Declarations**

**Funding**

No funding was received.

**Competing interests**

The authors declare that they have no competing interests.

**Availability of data and material**

The datasets analysed during the current study are available from the corresponding author on reasonable request.

**Code availability**

Not applicable.

**Ethics approval**

Our study complies with the Declaration of Helsinki and was approved by the local ethics committee.

**Consent to participate**

All patients gave written informed consent at the time of the CMR.

**Consent for publication**

Not applicable.
ACKNOWLEDGEMENTS

We thank Claudia Santarlasci for skillful secretarial work and all patients for their cooperation.

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Tables

Table 1. Demographic, clinical and CMR findings of the study population.
### Demographics

| Parameter                        | Value               |
|---------------------------------|---------------------|
| Age (years)                     | 63.76 ± 10.17       |
| Females, N (%)                  | 24 (24.0)           |

### Heart rate (bpm)

| State  | Value               |
|--------|---------------------|
| Rest   | 65.70±13.09         |
| Stress | 87.69±14.78         |

### End-systolic pressure (mmHg)

| State  | Value               |
|--------|---------------------|
| Rest   | 129.42±17.55        |
| Stress | 122.98±17.97        |

### Cardiovascular risk factors

| Condition         | Value   |
|-------------------|---------|
| Diabetes, N (%)   | 27 (27.0) |
| Hypertension, N (%)| 60 (60.0) |
| Dyslipidemia, N (%)| 56 (56.0) |
| Smoking, N (%)    | 24 (24.0) |
| Family history, N (%)| 49 (49.0) |
| At least one CVRF, N (%) | 92 (92.0) |

### Medical therapy

| Therapy          | Value   |
|------------------|---------|
| Diuretics, N (%) | 17 (17) |
| ACE-inhibitors, N (%) | 27 (27) |
| Sartans, N (%)   | 18 (18) |
| Aspirin, N (%)   | 62 (62) |
| Beta-blockers, N (%) | 44 (44) |

### CMR data

| Parameter          | Value               |
|--------------------|---------------------|
| LV EDVI (ml/m2)    |                     |
| Rest               | 80.33±20.22         |
| Stress             | 86.18±19.47         |
| LV ESVI (ml/m2)    |                     |
| Rest               | 33.19±16.89         |
| Stress             | 30.33±16.96         |
|                           |       |
|---------------------------|-------|
| **LV EF (%)**             |       |
| rest                      | 60.25±11.16 |
| stress                    | 66.36±11.85 |
| **ESPVR index (mmHg/mL/m2)** |       |
| rest                      | 4.84±2.47   |
| stress                    | 5.33±3.16   |
| **ΔESPVR index (mmHg/mL/m2)** |       |
|                           | 0.48±1.45   |
| **Myocardial fibrosis, N (%)** |   |
|                           | 46/85 (54.1) |
| **Stress CMR, N (%)**     |       |
| normal                    | 75 (75.0)   |
| perfusion defect          | 19 (19.0)   |
| perfusion+motion defect   | 6 (6.0)     |

N=number; CVRF=cardiovascular risk factor; LV=left ventricular; EDVI=end-diastolic volume index; ESVI=end-systolic volume index; EF=ejection fraction; ESPVR end-systolic pressure-volume ratio; ΔESPVR=delta end-systolic pressure-volume ratio; CMR=cardiac magnetic resonance.