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Exercise Stress Echocardiography and Tissue Synchronization Imaging of Myocardial Dyssynchrony

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Abstract

Background: Stress echocardiography represents one of the best possible imaging choice for the diagnosis and stratification of patients with coronary artery disease (CAD). However, this imaging technique presents some limitations such as the quality of the image, high inter-observer variability, and the operator-dependent expertise. New technologies have been recently developed to provide an objective, operator-independent, and quantitative analysis of regional myocardial function.

Objectives: The aim of this study was to investigate regional myocardial dyssynchrony using tissue synchronization imaging (TSI) during exercise stress echocardiography (ESE).

Patients and Methods: The ESE and TSI analysis of left ventricular (LV) segments was performed for 30 patients with CAD previously treated with revascularization therapy (CADr group) and the results were compared to those in 30 healthy subjects (norm group). The echo protocol comprised echocardiographic examinations at baseline, at the peak of exercise, and at 5 minutes after recovery as well as biplane and triplane acquisitions, pulsed wave of mitral flow, continuous wave of tricuspid regurgitation, tissue Doppler at the mitral annulus, TSI with an automatically detected positive time-to-peak velocity (Tp), and the measurement of the maximum activation time delay between myocardial segments and its standard deviation at baseline and peak stress for each patient.

Results: The CADr group showed a lower increase in E ($P = 0.005$), A ($P = 0.006$), S' ($P < 0.001$), and E' ($P = 0.006$) velocities at both baseline and peak stress and a significantly increased ventricular dyssynchrony at baseline and at peak stress ($P < 0.01$) compared to the norm group. The baseline-peak variations in the CADr group did not show significant differences. The relationships between the maximum activation delay and the other echocardiographic parameters showed a significant negative correlation with LV ejection fraction ($r = 0.217$; $P = 0.031$) and S' velocity ($r = -0.393$; $P < 0.001$) and a positive correlation with the E/E' ratio ($r = 0.376$; $P < 0.001$). The comparison between the different ischemic territories revascularized in terms of the delay in ventricular activation showed the greatest delay in the revascularized territory in 63% of the patients with ischemia.

Conclusions: The TSI analysis in patients with CAD may be considered an interesting parameter in addition to the conventional echocardiographic parameters during ESE.

Keywords: Coronary Artery Disease, Stress Echocardiography, Tissue Synchronization Imaging

1. Background

Stress echocardiography is the application of echocardiography to ischemic stress. This imaging technique represents the best (most cost-effective and risk-effective) possible imaging choice for the diagnosis and stratification of patients with coronary artery disease (CAD) (1). The stress echo signs of ischemia are a transient impairment in function induced by stress in a region contracting normally at baseline (regional dyssynergy) and reduced regional systolic wall thickening (2, 3).

However, this imaging technique presents some limitations such as its correlation with the quality of the image, high inter-observer variability, and the operator-dependent expertise, which might be overcome by appropriate training and the use of strict reading criteria (4, 5).

In order to overcome these limitations, scientists have developed new approaches to provide an objective, operator-independent, and quantitative analysis of regional myocardial function.

The most important new technologies recently developed to be applied to conventional echocardiography are tissue Doppler imaging (TDI) and its derivatives strain and strain rate, tissue synchronization imaging (TSI), and speckle-tracking echocardiography.

TSI is a noninvasive imaging technique dependent on TDI, and it can automatically measure the time-to-peak velocity (Tp) and peak velocity (Vp) of the myocardial left ventricle (LV). Velocities are represented with a color code, and different colors are used to qualitatively and quantitatively estimate systolic wall motion delays. In the early phase of

the contraction of the normal myocardium, Vp is encoded in green and there is no delay in movement (Tp = 20 - 150 msec). Delayed contracted myocardium is encoded in yellow or red, according to the degree of the delay. A moderate delay can be seen in yellow (Tp = 150 - 300 msec), and a severe delay can be seen in red (Tp = 300 - 500 msec) (6).

TSI was first applied to identify regional wall delay and to predict LV reverse remodeling after cardiac resynchronization therapy (7), but recent advances have demonstrated a relationship between the asynchronous motion of ischemic segments and LV function in patients with CAD (8).

Nonetheless, only a few studies have applied the TSI analysis to stress echocardiography for the detection of myocardial dyssynchrony in patients with CAD.

2. Objectives

The aim of this study was to investigate the application of the TSI analysis to exercise stress echocardiography (ESE), compared with echocardiographic parameters derived from conventional and TDI echocardiography, in patients with revascularized CAD (CADr) to highlight in particular the presence of an asynchronous contraction between revascularized and normal segments.

3. Patients and Methods

3.1. Study Population

This was a single-center, prospective study. Between April 2012 and July 2014, all consecutive subjects referred to our Echo Lab for an echocardiographic examination were prospectively enrolled. We selected 30 asymptomatic patients (26 men and 4 women, age 56.7 $\pm$ 10.1 years) with CAD who had been treated with revascularization therapy (percutaneous coronary intervention [PCI]) between 12 and 18 months before and who had a negative stress test in the previous 3 months. These patients formed the CADr group and were grouped according to the ischemic segments that were previously revascularized via PCI (Table 1). Twelve patients were treated for 1-vessel disease: 4 on the left anterior descending coronary artery (LAD), 4 on the right coronary artery (RCA), and 4 on the circumflex artery (CX). Fifteen patients underwent PCI for 2-vessel disease: 10 for the LAD and the RCA, 3 for the LAD and the CX, and 2 for the RCA and the CX. And finally, 3 patients were treated for 3-vessel disease. The control group (norm group) comprised 30 healthy subjects (23 men and 7 women, age 40.6 $\pm$ 17.5 years) with no history of ischemic heart disease (known or suspected) and with normal electrocardiograms and echocardiograms. These subjects were matched for anthropometric characteristics.

Table 1. Patients Grouped on the Basis of 1-, 2- or 3-Vessel Disease Treated

Disease	Patients, No. (%)
One-Vessel disease	
LAD	4 (13)
CX	4 (13)
RCA	4 (13)
Two-Vessel disease	
LAD + CX	3 (10)
LAD + RCA	10 (34)
CX + RCA	2 (7)
Three-Vessel disease	3 (10)

The exclusion criteria encompassed the presence of severe ventricular dysfunction (ejection fraction [EF] < 30%), severe valvular heart disease, respiratory distress, physical disability to perform the exercise stress test, occurrence of myocardial infarction within the previous 12 weeks, unstable angina, and supraventricular tachyarrhythmia. All the patients were subjected to a washout period of beta-blockers, nitrates, and channel calcium blockers before the stress test examination.

ESE was performed using a semi-supine bicycle ergometer with 25 Watts of incremental loading every 2 minutes up to:

- Muscle fatigue of the patient (symptom-limited test)
- Achievement of the maximum predicted heart rate
- Signs and/or symptoms prompting the suspension of the test

Electrocardiography and blood pressure were monitored using noninvasive methods at resting condition and each minute throughout the examination. All the patients signed a written consent before each procedure.

3.2. Echocardiographic Examination

All the subjects underwent echocardiographic examinations according to the recommendations of the American society of Echocardiography, the European association of cardiovascular imaging (ASE-EACVI) (9), at baseline (rest before stress), at the peak of exercise, and at 5 minutes after recovery, using a Vivid 7 ultrasound system (GE Healthcare, Horten, Norway), equipped with probe V3 matrix for multiplane acquisitions. The echo protocol was comprised of biplane acquisitions (parasternal long-axis and short-axis views) and triplane acquisitions (apical 4-, 3-, and 2-chamber views). All the views obtained were digitally stored.

In the triplane images, once the primary image plane was optimized similar to the one with the traditional 2D

transducer, the secondary image plane could then be automatically created in a quad-screen display. In this study, an apical 4-chamber view was chosen as the primary image plane. The matrix array transducer then allowed the visualization of the apical 4-, 2-, and 3-chamber views simultaneously. The frame rate was optimized with the acquisition of 3 heart cycles. For each patient, a triplane view was also acquired using the TDI technique.

3.3. Echo Parameters

3.3.1. Baseline

The baseline parameters were obtained in M-mode in the parasternal long-axis view. They comprised diastolic interventricular septal thickness, left ventricular diastolic and systolic internal diameters, left ventricular diastolic posterior wall thickness, and left ventricular mass indexed to body surface area.

3.3.2. Baseline, Exercise Peak, and Recovery

These parameters were comprised of LV end-diastolic and end-systolic volumes and LVEF. Pulsed-wave Doppler imaging parameters were obtained by placing the sample volume at the tip level of the mitral leaflets in the apical 4-chamber view and consisted of peak mitral inflow early diastolic velocity (E), late diastolic atrial filling velocity (A), their ratio (E/A), and E-wave deceleration time (DTE). TDI parameters were obtained by placing the sample volume of pulsed TDI at the septal and lateral mitral annulus and consisted of peak systolic myocardial velocity (S'), early (E') and late (A') diastolic myocardial velocities, and the E/E' ratio. Systolic pulmonary artery pressure (was derived from tricuspid regurgitation.

We also considered LV systolic and diastolic longitudinal functional reserve indices, obtained with Equations 1 and 2 (10):

$$\mathrm{LSR} = \Delta \mathrm{S'x}[1 - (\frac{1}{\mathrm{S'at\ rest}})] \quad (1)$$

Where LSR is left ventricular systolic longitudinal functional reserve index.

$$\mathrm{LDR} = \Delta \mathrm{E'x}[1 - (\frac{1}{\mathrm{E'at\ rest}})] \quad (2)$$

Where LDR is left ventricular diastolic longitudinal functional reserve index.

3.3.3. Tissue Synchronization Analysis

The TSI analysis was performed using commercially available software (Echo PAC, version 112.0.0, GE Healthcare, Milwaukee, WI) (Figure 1). This software, based on TDI, can automatically detect a positive Tp. The start of QRS complex, obtained with simultaneous electrocardiographic tracing, represented the start time of systole (T0). The TSI analysis among myocardial segments was performed using an LV segmentation of a 12-segment model; the apical segments of the heart were not taken into consideration in TSI since they were not optimally coded in color with this imaging tool (11).

For each patient, the maximum activation time delay was measured between myocardial segments, both at baseline and peak stress. Additionally, comparison was made between the most delayed myocardial segment, recognized by the bull's eye representation, and the correspondent segment of the perfusion territories of the 3 major coronary arteries: the LAD, RCA, and CX.

3.4. Statistical Analysis

The continuous variables are presented as means $\pm$ standard deviations (SD), while the dichotomous variables are described as frequencies and percentage. The normal distribution of the parameters was evaluated using the Shapiro-Wilk test. Parameters with a normal distribution were compared between the 2 groups using the student t-test, while the Mann-Whitney U test was used for the parameters with a non-Gaussian distribution. Relationships between the continuous parameters were assessed using the Pearson or Spearman method. All the tests were 2-tailed. $P < 0.05$ were considered statistically significant. The analyses were performed using SPSS software.

3.4.1. Reproducibility Analysis

The TSI analysis was performed by only 1 operator. The reproducibility of the measurements of TSI derived from TDI was performed in a subgroup of 10 randomly selected subjects and expressed as coefficient of variability (COV) and intraclass correlation coefficient (ICC) with 95% confidence intervals (CI). To assess intra-observer variability, the operator, who was blinded to the previous measurements, repeated the TSI analysis 1 week later.

4. Results

Reproducibility Analysis: acceptable intra-observer reproducibility, both for COV and ICC, was identified: (LVEF [%]: COV = 5.3 $\pm$ 1.7; ICC = 0.919 [CI, 0.674 - 0.980]).

The clinical data are presented in Table 2. The CADr group had significantly higher age (P = 0.001) and body mass index (P = 0.001) and lower metabolic equivalent (P = 0.003) and maximum workload achieved than expected (P = 0.045) than did the norm group. In the CADr group, the test was stopped for 10 patients due to fatigue, for 19 patients because they had achieved the maximum predicted heart rate, and for 1 patient owing to an abnormal increase in blood pressure. No patient had bundle branch block at rest or during exercise.

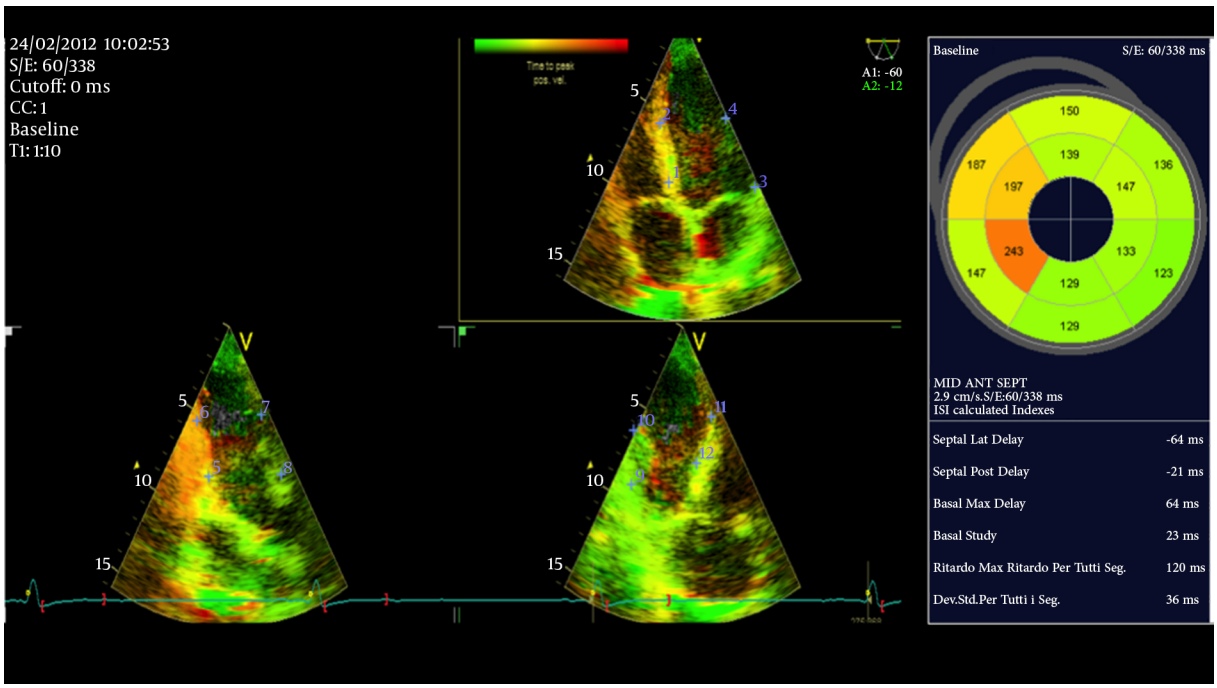

Figure 1. Tissue Synchronization Analysis

Table 2. Clinical Characteristics of the Study Population

Clinical Characteristics	CADr (n = 30)	Norm (n = 30)	P Value
Age, y	56.7 ± 10.1	40.6 ± 17.5	0.001
Sex			0.070
Male	26	23	
Female	4	7	
BSA, m^2	1.94 ± 0.20	1.83 ± 0.21	0.086
BMI, kg/m^2	26.7 ± 3.4	23.5 ± 2.5	0.001
METS	5.0 ± 1.4	7.0 ± 2.6	0.003
MWEa, %	81.8 ± 7.1	86.0 ± 6.7	0.045

Table 3. Echocardiographic Parameters at Baseline

Parameters	CADr	Norm	P Value
LV IVSd, mm	8.4 ± 1.1	8.3 ± 1.5	0.733
LV IDd, mm	50.9 ± 8.3	45.6 ± 7.1	0.024
LV IDs, mm	34.0 ± 7.1	27.7 ± 5.4	0.001
LV PWd, mm	8.8 ± 1.5	8.8 ± 1.6	0.848
LV Mi, g/m2	84.1 ± 28.0	71.7 ± 20.1	0.097
LV EDV, mL	93.6 ± 30.8	83.1 ± 31.9	0.100
LV ESV, mL	40.2 ± 19.9	32.1 ± 14.8	0.140
LV EF, %	59.2 ± 8.7	61.7 ± 5.0	0.215
E velocity, cm/sec	65.3 ± 15.2	75.1 ± 21.5	0.113
E Dec. Time, msec	219.6 ± 54.4	207.9 ± 77.1	0.529
A velocity, cm/sec	71.5 ± 16.7	52.3 ± 13.8	< 0.001
E/A ratio	0.95 ± 0.25	1.52 ± 0.58	< 0.001
S', cm/sec	7.8 ± 1.9	9.2 ± 2.3	0.066
E', cm/sec	9.2 ± 2.1	13.2 ± 3.9	< 0.001
A', cm/sec	9.3 ± 2.4	7.6 ± 2.7	0.024
E/E'	7.2 ± 1.7	5.8 ± 1.1	0.002
PAPs, mm Hg	17.2 ± 7.1	18.3 ± 7.2	0.830

4.1. Echocardiographic Parameters

Table 3 depicts the echocardiographic parameters at baseline. The CADr group had significantly higher LV systolic internal diameter (P = 0.001), higher A values (P < 0.001), lower E/A ratio (P < 0.001), lower E' values (P < 0.001), and higher E/E' ratio (P = 0.001) than did the norm group. Only 4 patients in the CADr group had EF < 50%. (One patient had EF = 38% and 3 patients had EF = 48%.)

Table 4 illustrates the echocardiographic parameters at the peak of exercise. The CADr Group showed significantly lower values of E (P = 0.001), E/A (P = 0.004), S' (P =

0.001), and E' ($P < 0.001$) than did the norm group. Fifteen patients in the CADr group had an increase of EF < 10%, and EF in 2 patients was maintained at < 50%.

Table 4. Echocardiographic Parameters at Peak Stress

Parameters	CADr	Norm	P Value
LV EDV, mL	94.9 ± 29.3	78.2 ± 31.0	0.060
LV ESV, mL	34.9 ± 17.0	25.6 ± 11.7	0.049
LV EF, %	65.6 ± 9.5	68.4 ± 5.9	0.260
E velocity, cm/sec	97.8 ± 24.9	126.7 ± 32	0.001
E Dec. Time, msec	182 ± 75.8	140.2 ± 68.1	0.038
A velocity, cm/sec	95.2 ± 23.2	97.5 ± 31.2	0.773
E/A ratio	1.07 ± 0.34	1.37 ± 0.39	0.004
S', cm/sec	11.1 ± 3.3	16.1 ± 3.7	0.001
E', cm/sec	13.8 ± 3.2	20.5 ± 5.8	< 0.001
A', cm/sec	12.8 ± 4.4	13.2 ± 3.8	0.757
E/E'	7.0 ± 2.2	6.5 ± 1.9	0.372
PAPs, mm Hg	18.5 ± 6.8	21.1 ± 8.1	0.608

Table 5 demonstrates the difference between baseline and peak (Δ) for each group. The CADr group had a lower increase in E ($P = 0.005$), A ($P = 0.006$), S' ($P < 0.001$), and E' ($P = 0.006$) velocities at peak stress with respect to the baseline than did the norm group. Furthermore, LV LSR and LDR indices had a lower increase in the CADr group than in the norm group (LSR: $P < 0.001$ and LDR: $P = 0.003$).

Table 5. Differences Between Baseline and Peak Stress Echocardiographic Parameters

Parameters	CADr	Norm	P Value
LV EDV, mL	1.3 ± 22.0	-4.9 ± 21.9	0.333
LV ESV, mL	-5.3 ± 13.4	-6.5 ± 9.9	0.733
LV EF, %	6.4 ± 7.5	6.7 ± 5.0	0.552
E-wave velocity, cm/sec	31.9 ± 24.9	51.7 ± 19.6	0.005
E Dec. Time, msec	-34.0 ± 83.8	-67.7 ± 93.1	0.192
A-wave velocity, cm/sec	23.6 ± 23.9	45.3 ± 28.3	0.006
E/A ratio	0.09 ± 0.41	-0.15 ± 0.49	0.071
S', cm/sec	3.2 ± 2.3	6.9 ± 3.9	< 0.001
E', cm/sec	4.6 ± 2.5	7.4 ± 4.4	0.006
A', cm/sec	3.5 ± 4.1	5.6 ± 4.4	0.101
E/E'	-0.2 ± 2.4	0.7 ± 1.5	0.152
PAPs, mm Hg	1.3 ± 3.0	2.5 ± 3.9	0.355
LV LSR	2.8 ± 2.0	6.1 ± 3.3	< 0.001
LV LDR	4.1± 2.3	6.8 ± 4.0	0.003

Table 6 shows the TSI analysis. The CADr group, compared to the norm group, had a significantly increased ventricular dyssynchrony, both at baseline (99.0 ± 48.4 vs. 60.5 ± 39.7 msec) and at peak stress (98.2 ± 38.8 vs. 60.1 ± 24.5 msec) ($P < 0.01$ for each parameter). However, only 5 patients in the CADr group had a moderate delay at baseline (ranging from 157 to184 ms) and 3 patients at peak (ranging from 154 to 167 msec); none had a severe delay. The CADr group showed no significant variations of TSI at peak stress compared to the baseline.

Table 6. Tissue Synchronization Analysis (Baseline and Peak Stress)[a]

Parameters	CADr	Norm	P Value
Maximum activation time delay SD, msec			
Baseline	32.2 ± 17.5	19.5 ± 14.2	0.009
Peak stress	36.3 ± 17.2	20.8 ± 8.7	0.001
Δ Baseline-peak	2.9 ± 22.2	1.3 ± 14.3	0.772
Maximum activation time delay among segments, msec			
Baseline	99.0 ± 48.4	60.5 ± 39.7	0.007
Peak stress	98.2 ± 38.8	60.1 ± 24.5	< 0.001
Δ Basline-peak	-4.0 ± 55.2	-0.4 ± 37.2	0.798

[a] P value CADr vs. norm.

The comparison between the different ischemic territories revascularized in terms of the delay in ventricular activation, analyzed by segmental analysis with TSI, showed that the most delayed segment corresponded to the revascularized territory in 63% of the ischemic patients.

Finally, the relationship between the maximum activation delay and the other echocardiographic functional parameters showed a significant negative correlation with LVEF ($r = 0.217$; $P = 0.031$) (Figure 2, Panel A) and S' ($r = -0.393$; $P < 0.001$) (Figure 2, Panel B) and a positive correlation with the E/E' ratio ($r = 0.376$; $P < 0.001$) (Figure 2, Panel C).

5. Discussion

The asynchronous motion of the LV is obvious in patients with CAD. Delayed contractions of myocardium, decreased contraction force and dyssynchronous motion represent impaired ventricular function.

The synchronization analysis with TSI showed that the delayed contraction of the myocardium was significantly increased in the CADr group compared to the norm group, although the global function, expressed by EF, was preserved. This condition caused increased ventricular

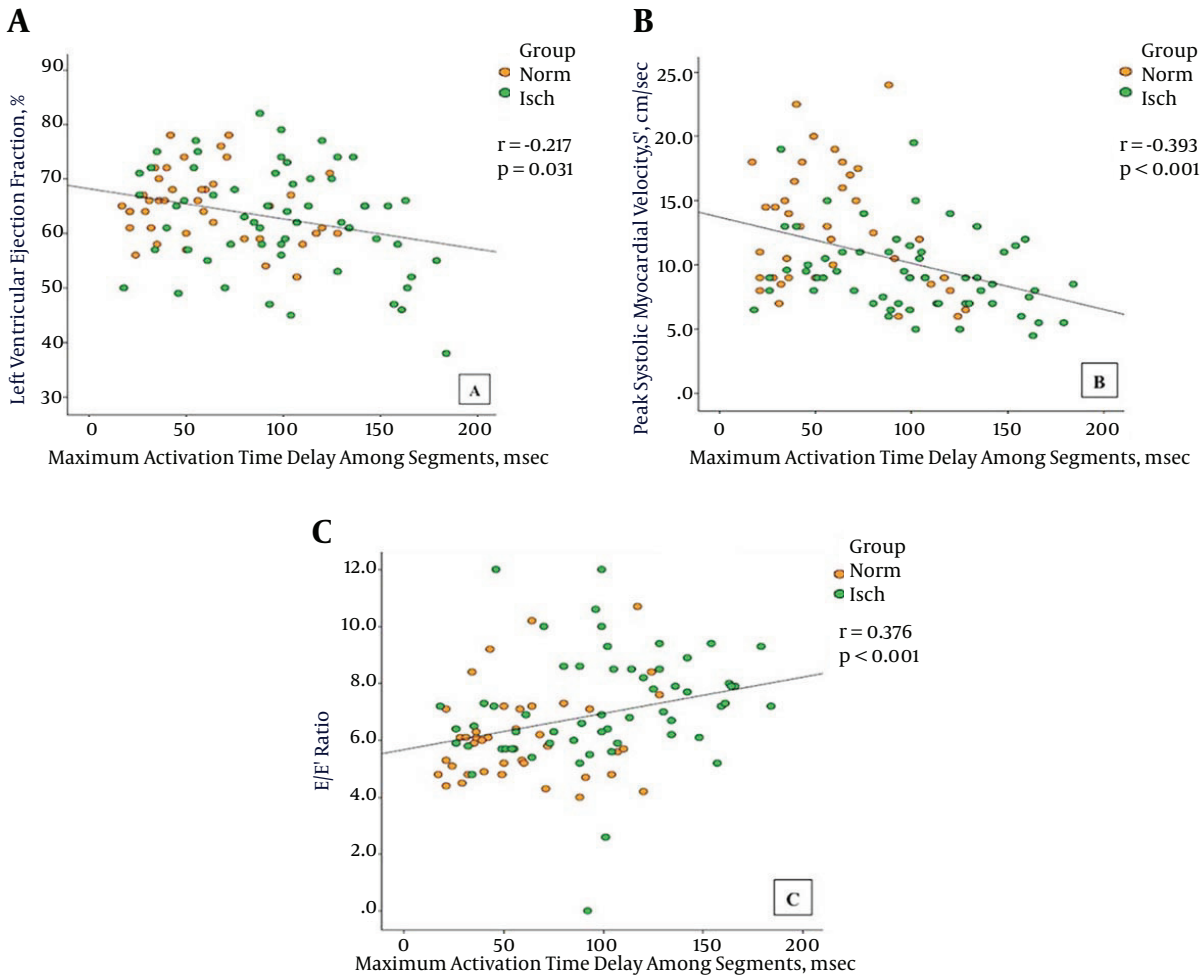

Figure 2. Relationship Between the Maximum Activation Delay and the Other Echocardiographic Functional Parameters

dyssynchrony in these patients. Furthermore, we demonstrated that in 63% of the patients in the CADr group, there was still activation delay in the revascularized segments. These myocardial segments, despite revascularization, contracted belatedly compared to the other ventricular segments.

This condition can be explained by several pathophysiological hypotheses:

a) Persistence of a residual ischemia that impairs the systolic wall thickening; it causes an asynchronous contraction between ischemic and the normal regions (12).

b) Subendocardial fibrosis, resulting from ischemic damage, which induces a delayed activation of segments included in the fibrotic scar. Indeed, the synchronous motion among ventricular segments, required to maintain the normal blood pumping, depends on a normal myocardial conduction-contraction system, so their impairment, produced by ischemia or hypoxia, can prolong significantly the conduction time of ischemic segments and reduce their contractive function (9).

The comparison between the results obtained by the TSI analysis and the other echocardiographic parameters (conventional and derived from TDI) conferred important evidence regarding the impairment of diastolic and systolic ventricular functions.

First, all the patients in the CADr group during the stress test showed sub-clinical alterations in ventricular performance, assessable by the E/E' ratio, a parameter that represents a good surrogate for LV filling pressure (13). We found that it was significantly increased with the increasing of segment delays identified by TSI (P = 0.001) and that it expressed impaired diastolic function in the CADr group.

Furthermore, we observed that maximum segment delay was negatively related both to the global function and

to the longitudinal contractile function of the LV, represented by LVEF and peak systolic myocardial velocity (S'), respectively, in the CADr group. In fact, the increase in segment delay corresponded to a decrease in EF and S'. However, we found a more significant decrement in S' ($P < 0.001$ vs. $P = 0.031$), which proves that it can represent a more accurate parameter of myocardial contraction than does LVEF. According to Russell et al. (14) indeed, in ventricles with regional differences in contractility, as in ischemia, some segments are stretched in systole, whereas others contract, resulting in a dyssynchronous contraction pattern. The result of this dyssynchrony is that a substantial amount of LV work is wasted on stretching the opposing segments and, therefore, does not contribute effectively to LV ejection.

Only a few studies published in the literature have been performed to detect ischemia and assess regional motion abnormality in CAD using the TSI technique.

Tian et al. (8) used TSI to evaluate regional myocardial dyssyncronicity in 60 patients with CAD compared with 40 healthy subjects with synchronous myocardial. The authors identified an abnormal myocardial synchrony pattern in the ischemic patients.

Recently, Tas et al. (15) performed a study including 25 healthy subjects and 25 patients positive for ischemia, combining dobutamine stress echocardiography (DSE) and TSI. Their results showed that stress and ischemia did not create any significant difference over the interventricular dyssynchrony with DSE, although at the segmental level it prolonged the time to peak systolic velocity. However, these alterations did not show any significant difference between the healthy group and the positive DSE subjects.

Similarly, the patients in the CADr group in our study showed a significant increase in ventricular dyssynchrony, both at rest and at peak exercise, while the rest-peak differences did not present significant variations between the 2 groups.

This evidence would suggest the possibility to assess changes intra- and inter-segmental at rest and at peak of stress to highlight a difference more precise than evaluation of the maximum delay.

In conclusion, the analysis of ventricular function in patients with myocardial ischemia has important implications for the prognostic stratification and the optimization of the therapy. TSI provides a visual detection of abnormal myocardial motion, even in a subclinical phase. We think that the study of myocardial dyssynchrony may be considered an interesting parameter for the evaluation of ischemic and infarcted segments in patients with CAD in addition to the conventional echocardiographic parameters, although its relevance during ESE must still be improved.

5.1. Study Limitations

First and foremost among the limitations of the present study is that the TSI method does not detect the apical segments of the heart; consequently, we did not study patients with apical wall motion abnormalities. Another limitation is that we did not consider the wall motion score index and its relation with TSI. Moreover, since the patency of the coronary arteries after PCI was available only in 11 patients, we did not take these data into consideration. Given the small sample size of this study, longitudinal assessments are required to confirm the prognostic impact of these results.

Footnotes

Authors' Contribution: Study concept and design, Ines Paola Monte; acquisition of data, Ines Paola Monte, Veronica Bordonaro; analysis and interpretation of data, Ines Paola Monte, Sergio Buccheri; drafting of the manuscript, Veronica Bordonaro; critical revision of the manuscript for important intellectual content, Ines Paola Monte, Corrado Tamburino; statistical analysis, Sergio Buccheri.

Conflict of Interest: The authors declare that there is no conflict of interest.

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