



# Left ventricular mechanical dyssynchrony in patients with chest pain and normal epicardial coronary arteries

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**Background.** To detect ischemia in patients with angina and normal coronaries frequently represents a complex diagnosis.

**Methods.** To investigate whether left ventricular mechanical dyssynchrony by phase analysis contributes in the evaluation of patients with chest pain and normal coronaries, gated-SPECT myocardial perfusion imaging (MPI) at rest and 30 minutes post-stress was performed in 218 patients with normal epicardial coronaries, who were divided into two groups: those with summed difference score (SDS)  $\geq 4$  (54 patients, Group 1), and those with SDS  $< 4$  (164 patients, Group 2). Intraventricular synchronism-phase standard deviation (PSD) and histogram bandwidth (HBW)—was evaluated by phase analysis.

**Results.** Women were significantly more frequent in Group 2 (those without ischemia in SPECT MPI): 113 (69%) vs 25 (46%),  $P = .00001$ . In males, left ventricular ejection fraction (LVEF) and ventricular volumes were not significantly different between patients with or without ischemia. However, ischemic females showed significantly higher ventricular volumes, minor post-stress LVEF and more negative delta LVEF ( $-3.9$  vs  $0.34$ ,  $P = .0008$ ) than the non-ischemic ones. There was a significant post-stress increase of PSD and HBW among males, although not among females. According to SSS ( $\geq 4$ , with ischemia/necrosis;  $< 4$ , without ischemia/necrosis), post-stress PSD and HBW significantly increase both in male and female, and PSD and HBW were significantly higher in females with SSS  $\geq 4$  compared to those with SSS  $< 4$  (PSD rest:  $19.04^\circ$  vs  $11.72^\circ$ ,  $P < .0001$ ; HBW rest:  $58.85^\circ$  vs  $38.21^\circ$ ,  $P < .0001$ ). PSD and HBW were also higher among males with SSS  $\geq 4$  compared to those with SSS  $< 4$ , although not significantly.

**Conclusion.** Higher ventricular volumes in females and dyssynchrony are associated with inducible ischemia in MPI in patients with chest pain and normal coronaries. Stress-induced ischemia increases degree of dyssynchrony.

**Key Words:** Myocardial perfusion imaging • intraventricular dyssynchrony • ischemia • normal coronary arteries • gated-SPECT

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The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

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**Abbreviations**

CAD	Coronary artery disease
ESV	End-systolic volume
EDV	End-diastolic volume
HBW	Histogram bandwidth
LVEF	Left ventricular ejection fraction
MPI	Myocardial perfusion imaging
PSD	Phase standard deviation
SDS	Summed difference score
SRS	Summed rest score
SSS	Summed stress score

**See related editorial, pp. 1064–1067**

**INTRODUCTION**

To detect a true ischemia in patients with angina and normal epicardial coronary arteries frequently represents a complex diagnosis. Taking into account that, in these patients, endothelial dysfunction and microvascular angina are quite common findings, it is important to adequately assess the presence of ischemia.

Gated-SPECT myocardial perfusion imaging (MPI) is the only imaging technique able to provide, in a very reproducible way, information about global and regional ventricular function, myocardial perfusion and ventricular dyssynchrony using the same test.

Left ventricular (LV) dyssynchrony assessed by phase analysis from gated-SPECT MPI is a valid tool<sup>1</sup> with additional potential benefits such as its widespread availability, reproducibility and repeatability.<sup>2,3</sup> Quantitative indices given by phase analysis, such as phase standard deviation (PSD) and histogram bandwidth (HBW), correlate well with LV dyssynchrony measured by tissue Doppler imaging,<sup>4-6</sup> and have been shown to predict response to cardiac resynchronization therapy in patients with heart failure.<sup>7</sup>

The mechanisms which generate dyssynchrony are the temporal delay of the mechanical contraction in patients with wide QRS and the disparities in the contraction seen in ischemia and fibrosis.<sup>8</sup> Stress-induced myocardial ischemia causes dyssynchronous contraction in the ischemic region. It has been reported that differences in the dyssynchrony pattern between ischemic and normal myocardial post-stress may aid the diagnosis of coronary artery disease (CAD) using both <sup>201</sup>Thallium<sup>7</sup> and <sup>99m</sup>Tc Technetium-sestamibi-gated-SPECT MPI.<sup>8</sup>

Specifically, in patients with normal coronary arteries, Karacalioglu et al. showed that LV mechanical dyssynchrony assessed by phase analysis can be considered as new evidence supporting the concept that an abnormal scintigraphy finding, rather than being false-positive, may be an early marker of vasomotion changes

associated with atherosclerosis in patients with normal coronary angiography findings.<sup>9</sup>

Thus, taking into account that there is very scarce evidence of this, the aim of this study was to investigate whether the LV mechanical dyssynchrony by phase analysis helps in the diagnosis assessment of patients with chest pain and normal coronary arteries.

**MATERIALS AND METHODS****Study Population**

We studied 218 patients (mean age: 57 ± 11 years, 63% women), with stress-rest gated-SPECT MPI and normal epicardial coronary arteries by invasive coronary angiography in the previous 6 months who were referred by their attending physicians to the Nuclear Medicine Department of the Institute of Cardiology from April 2014 to April 2016.

Regarding coronary risk factors, the following were considered: diabetes mellitus: fasting blood glucose ≥ 5.55 mmol·L<sup>-1</sup> (≥ 100 mg·dL<sup>-1</sup>) or treatment for diabetes; dyslipidemia: fasting plasma triglycerides ≥ 1.70 mmol·L<sup>-1</sup> (≥ 150 mg·dL<sup>-1</sup>) and/or HDL cholesterol <1.29 mmol·L<sup>-1</sup> (< 50 mg·dL<sup>-1</sup>); high blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg or anti-hypertensive treatment; smoking habit: smokers in the year before the study.

These patients were divided into two groups: those with SDS ≥ 4 (54 patients, Group 1) and those with SDS < 4 (164 patients, Group 2). Each patient underwent a <sup>99m</sup>Tc methoxy-isobutyl-isonitrile gated-SPECT MPI, following a two-day protocol: exercise stress/rest, including left ventricular dyssynchrony assessment by phase analysis.

This study complies with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions. The review board and ethics committee of the Institute of Cardiology approved the study, and written informed consent was obtained from all patients prior to their inclusion in the study.

**Gated-SPECT MPI**

The first day of the study all patients underwent a symptom-limited treadmill exercise stress test (MTM-1 500 med, Schiller, Switzerland) following the Bruce protocol. At peak exercise, a mean dose of 15 mCi of <sup>99m</sup>Tc methoxy-isobutyl-isonitrile was administered intravenously, and the patient continued to exercise for an additional period of 60–90 seconds when possible. Post-stress images were acquired at 30 minutes after tracer injection, using a rotating dual-head gamma camera (Nucline Spirit DHV, Mediso, Hungary) equipped with low-energy, high-resolution, parallel-hole collimators, with a 20% energy window centered on the 140 keV photopeak. Sixty-four projections (20 seconds per projection), eight frames/cycle, with a 64 × 64 matrix, were obtained over a 180 degrees' orbit. The following day, rest images were acquired at 30 minutes after the intravenous injection of a

mean dose of 15 mCi of <sup>99m</sup>Tc methoxy-isobutyl-isonitrile. Imaging was always performed in a supine position.

All images were reconstructed using OSEM with three iterations and ten subsets and filtered by a Butterworth filter, power 10, using a cut-off frequency of 0.3 cycles/mm. No attenuation or scatter correction was applied. All patients were studied 72 hours after the withdrawal of cardiovascular medication.

### SPECT Image Interpretation

Semi-quantitative visual interpretation of images employed short-axis and vertical long-axis tomograms divided into 17 segments.<sup>10</sup> Each segment was scored by the consensus of two expert independent observers who were unaware of the clinical and angiographic data, using a five-point scoring system (from 0 = normal to 4 = absence of myocardial uptake). Disagreements, including any score in each SPECT segment, were resolved by consensus.

Segments with reduced tracer uptake were considered to be reversible defects if the score decreased  $\geq 1$  point from stress to rest. Summed stress score, summed rest score and summed difference score (SSS, SRS and SDS) were obtained. If the summed difference score was 4 or greater it was considered as presence of stress-induced ischemia.

The assessment of regional wall motion (WM) was performed by visual inspection of gated tomograms in cine mode for semi-quantitative scoring. The LV myocardium was divided into 17 segments. Segmental WM was classified as: normal, hypokinesis, akinesis or dyskinesis. An operator-independent analysis of regional WM and left ventricular ejection fraction (LVEF) was made using dedicated software (Emory Cardiac Toolbox-ECTb-, Syntermed, Inc., Atlanta, Georgia, USA). The difference between LVEF from post-stress and rest acquisitions was defined as Delta LVEF (Delta LVEF = post-stress LVEF – rest LVEF). The left intraventricular mechanical dyssynchrony was evaluated at rest and post-stress using the phase analysis of the gated-SPECT MPI included in the ECTb, previously described.<sup>1</sup>

### Statistical Analysis

Categorical variables are expressed as numbers and percentages, and compared when necessary with the chi-square test and the Fisher's exact test. Continuous variables are expressed as mean  $\pm$  standard deviation (SD), and the non-parametric Kolmogorov–Smirnov normality test (K-S test) was applied to check variables normality. For independent observations, the nonpaired Student's *t* test, or the Mann–Whitney U test were applied. A value of  $P < .05$  was considered significant. The statistical review of the study was performed by a biomedical statistician.

## RESULTS

### Patient Characteristics

Clinical characteristics of patients are shown in Table 1.

Women were significantly more frequent in Group 2 (those without ischemia in SPECT MPI): 113 (69%) vs 25 (46%),  $P = .00001$ . There were no significant differences between both groups regarding age and presence of coronary risk factors.

Characteristics of chest pain as symptom referred by the patients before the gated-SPECT were not significantly different between both groups: typical chest pain, 48% vs 43%; atypical, 30% vs 35%, and no pain in 20% vs 21% (Groups 1 vs 2).

### Stress Results

Stress characteristics are presented in Table 2.

There was no significant difference between both groups in exercise duration, METS and percentage of maximal heart rate (MHR) achieved.

**Table 1.** Patient characteristics

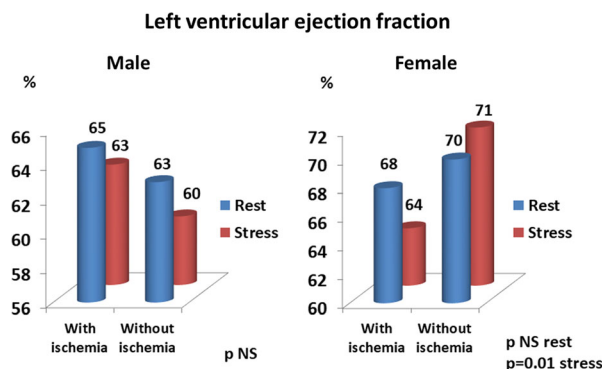
	<b>Group 1 (n = 54)</b>	<b>Group 2 (n = 164)</b>	<b>P value</b>
Sex (M/F)	29/25	51/113	0.000014
High blood pressure	44 (81%)	125 (76%)	NS
Diabetes mellitus	10 (19%)	37 (23%)	NS
Dyslipidemia	18 (33%)	60 (36%)	NS
Smoking habit	24 (44%)	53 (32%)	NS
Family history of CAD	1 (2%)	2 (1%)	NS

Variables are expressed as number of patients and percentage in parenthesis, except sex (number of patients) CAD, coronary artery disease; F, female; M, male

**Table 2.** Stress characteristics

	<b>Group 1 (n = 54)</b>	<b>Group 2 (n = 164)</b>	<b>P value</b>
Exercise duration (min)	8 ± 2	7 ± 2	NS
METS	6.13 ± 1.97	6.41 ± 1.67	NS
% MHR achieved	92 ± 7	93 ± 8	NS

Values are expressed as mean ± SD  
MHR, maximal heart rate



**Figure 1.** Left ventricular ejection fraction behavior according to sex. Post-stress left ventricular ejection fraction was significantly higher in female patients with negative SPECT MPI, ( $P < 0.01$ ). MPI, myocardial perfusion imaging.

### Gated-SPECT MPI

**Myocardial perfusion and left ventricular function** SSS values were:  $8.20 \pm 5.03$  (Group 1) vs  $3.29 \pm 4.74$  (Group 2),  $P < .0001$ . SRS was  $2.98 \pm 3.83$  (Group 1) vs  $2.43 \pm 4.27$  (Group 2), pNS. SDS values were:  $5.66 \pm 1.84$  vs  $0.62 \pm 1.39$  (Groups 1 vs 2,  $P < .0001$ ). The mean transient ischemic dilatation ratio was higher in Group 1: 1.06 (Group 1) vs 1.0 (Group 2),  $P = .04$ .

Considering the sex differences in LVEF, ventricular volumes and intraventricular synchronism, these variables are presented separately in male and female patients. In males, LVEF and ventricular volumes were not significantly different between patients with or without ischemia (Figures 1 and 2). However, ischemic females showed significantly higher ventricular volumes, minor post-stress LVEF and more negative delta LVEF (LVEF post-stress more reduced than LVEF at rest) than the non-ischemic ones (Figures 1 and 2).

**Intraventricular synchronism** Intraventricular synchronism parameters (PSD and HBW) were not different between ischemic and non-ischemic patients (Figures 3 and 4). However, there was a significant post-stress increase of PSD and HBW among males

(Figure 3), although not among females (Figure 4). Nevertheless, when we analyzed MPI studies according to SSS ( $\geq 4$ , with ischemia/necrosis;  $< 4$ , without ischemia/necrosis), post-stress PSD and HBW significantly increased both in male and female, and PSD and HBW were significantly higher in females with SSS  $\geq 4$  compared to those with SSS  $< 4$  (Table 3). PSD and HBW were also higher among males with SSS  $\geq 4$  compared to those with SSS  $< 4$ , although not significantly (Table 3).

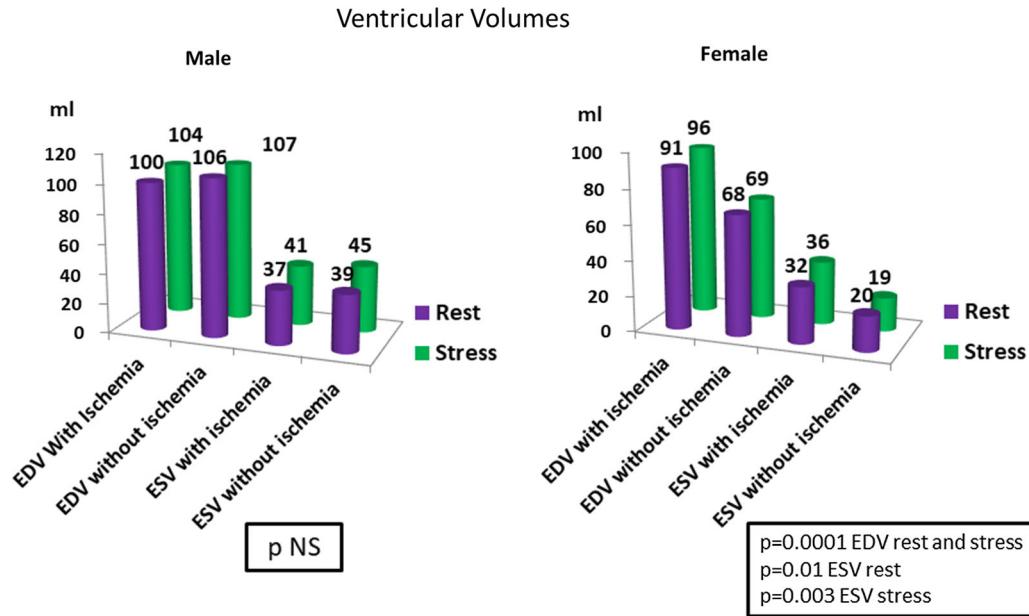
## DISCUSSION

### Myocardial Perfusion and Left Ventricular Function

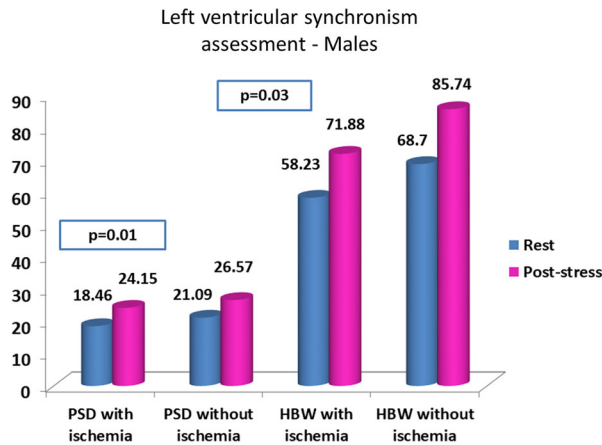
Our results show that in male patients with chest pain, normal epicardial coronary arteries and inducible ischemia, both PSD and HBW indices of intraventricular dyssynchrony increase significantly post-stress. When extension of ischemia and necrosis/fibrosis are considered based on the SSS values, post-stress PSD and HBW significantly increase both in male and female, and PSD and HBW are higher in patients with SSS  $\geq 4$  compared to those with SSS  $< 4$ , being significant in females. As far as we know, this is the first paper comparing synchronism assessment in patients with chest pain and normal coronaries according to MPI results.

Gated-SPECT offers the ability to assess perfusion and function using the same test. It has been reported that in patients who have typical exertional angina and a positive exercise stress test without significant coronary stenosis, coronary microcirculation abnormalities have been shown to play a pathophysiological role.<sup>11,12</sup> Our group has shown that stress-induced ischemia is associated with post-stress LVEF reduction in postmenopausal women with typical angina, normal coronary angiography, and a trend toward abnormal endothelial-mediated vasodilation.<sup>13,14</sup>

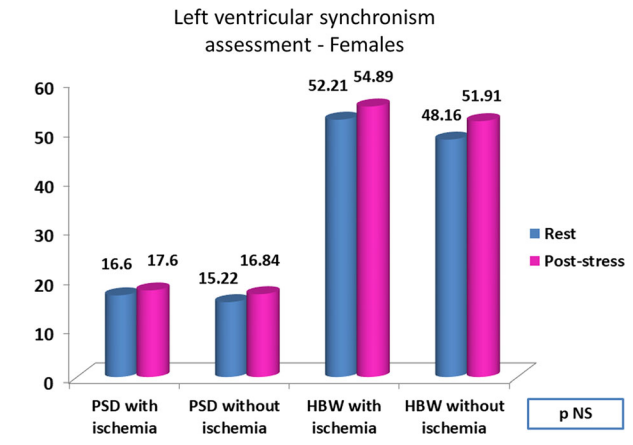
In the present study, post-stress LVEF was significantly reduced in ischemic females compared to the non-ischemic ones, with a mean delta LVEF of  $-3.9$  vs



**Figure 2.** Ventricular volumes behavior according to sex. Mean end-diastolic and end-systolic volumes are presented according to the presence or not of inducible ischemia on MPI. Both end-diastolic and end-systolic volumes were significantly higher in female patients with ischemia. *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *MPI*, myocardial perfusion imaging.



**Figure 3.** Left ventricular synchronism assessment in male patients. Post-stress intraventricular synchronism parameters (*PSD* and *HBW*) significantly increased in ischemic patients. Normal values for men are: *PSD*:  $14.2 \pm 5.1^\circ$ , *HBW*:  $38.7 \pm 11.8^\circ$ , Ref. [1]. *HBW*, histogram bandwidth; *PSD*, phase standard deviation.



**Figure 4.** Left ventricular synchronism assessment in female patients. Intraventricular synchronism parameters (*PSD* and *HBW*) did not change significantly between groups. Normal values for women are: *PSD*:  $11.8 \pm 5.2^\circ$ , *HBW*:  $30.6 \pm 9.6^\circ$ , Ref. [1]. *HBW*, histogram bandwidth; *PSD*, phase standard deviation.

0.34, and the ventricular volumes were significantly higher. This is likely due to the fact that Group 1 patients had ischemia detected by MPI and thus may suffer from a more extensive microvascular disease compared to Group 2.

Borderline to mild perfusion abnormalities have been reported in up to 27% of selected patients with

angina and normal findings on coronary angiography.<sup>15,16</sup> In the present work, both *SSS* and *SDS* were significantly greater in Group 1 than in Group 2.

Normal limits of *LVEF* may be higher in individuals with a low body mass index (e.g. women and certain ethnicities) as well as volumes are smaller.<sup>17</sup> Phase analysis of data from the Japanese Society of

**Table 3.** Intraventricular synchronism according to sex and summed stress score

<b>Male</b>	<b>SSS ≥ 4 n = 32</b>	<b>SSS &lt; 4 n = 54</b>	<b>P</b>
PSD at rest	20.35 ± 15.25°	14.33 ± 4.75°	NS
PSD at stress	26.32 ± 17.97° *	18.93 ± 9.38°	NS
HBW at rest	66.69 ± 51.84°	43.84 ± 11.48°	NS
HBW at stress	81.61 ± 66.39° **	57.23 ± 21.70°	NS
<b>Female</b>	<b>SSS ≥ 4 n = 30</b>	<b>SSS &lt; 4 n = 102</b>	<b>P</b>
PSD at rest	19.04 ± 10.70°	11.72 ± 3.33°	< .0001
PSD at stress	21.18 ± 12.42° ***	11.98 ± 4.58°	< .0001
HBW at rest	58.85 ± 27.24°	38.21 ± 10.28°	< .0001
HBW at stress	64.90 ± 35.56° ****	37.89 ± 10.70°	< .0001

Values are expressed as mean ± SD  
 PSD, phase standard deviation; HBW, histogram bandwidth  
 \*P = .0004 (post-stress vs rest); \*\*P = .005 (post-stress vs rest); \*\*\*P = .04 (post-stress vs rest); \*\*\*\*P = .03 (post-stress vs rest)

Nuclear Medicine working group (JSNM-WG) normal databases for gated-SPECT using <sup>99m</sup>Tc-labeled compounds<sup>18,19</sup> identified that phase parameters are larger in men. Some explanations for this can be considered: myocardial activity (counts/cm<sup>3</sup>) could be lower in men than in women, due to a larger myocardial volume; the same filtering might result in smoother images in women than in men; electrical depolarization of the heart takes longer time because the mass of the male heart is larger. In addition, exercise intensity could be higher for men than for women, which could affect phase values.<sup>20</sup> Thus, the results of the present work have been analyzed separately according to sex. Consequently, LVEF values were higher in women and ventricular volumes were smaller. With respect to ventricular volumes, it is important to point out that female patients with inducible ischemia had significantly higher end-diastolic volume (EDV) and end-systolic volume (ESV) compared to those without ischemia. Thus, there are differences in left ventricular volumes that are associated with stress-induced ischemia, which may be explained by the possibility of the presence of microvascular endothelial dysfunction with normal epicardial coronaries.<sup>21,22</sup>

**Intraventricular Synchrony**

It has been shown that both PSD and HBW, obtained by Fourier phase analysis in a gated-SPECT MPI, allow the assessment of intraventricular synchrony.<sup>1,23,24</sup>

Karacalioglu et al<sup>9</sup> studied 32 patients with reversible mild perfusion defects on MPI and normal coronary angiogram. They found that measurements of PSD and PHB were significantly higher than those reported in the literature, and concluded that the presence of LV mechanical dyssynchrony supports the concept that an abnormal scintigraphy finding, rather than being false-positive, may be an early marker of vasomotion changes associated with occult atherosclerosis in these patients.

In agreement with this, our study showed a greater degree of dyssynchrony based on PSD and HBW in male patients with inducible ischemia compared to those with normal perfusion. But this was still more significant in male and female patients when the extent of both ischemia and necrosis/fibrosis were considered. Hida et al<sup>8</sup> reported that the mechanisms responsible for dyssynchrony are temporal contraction delay (as in left bundle branch block) and heterogeneous contraction due to fibrosis and ischemia. This could explain our results.

Interestingly, it has been reported that during the cardiac aging process, women are more likely to preserve myocardial mass and structure, whereas men tend to have greater myocyte cell loss and cellular reactive hypertrophy. These sex-related differences may also reflect different mechanisms of dyssynchrony induction.<sup>25</sup> Liu et al have noted that women have greater myocardial interstitial fibrosis.<sup>26</sup> In a large multi-ethnic cohort of 1392 asymptomatic participants in the Multi-Ethnic Study of Atherosclerosis (MESA; mean age: 64.7 years; 46% women) studied by cardiac

magnetic resonance (CMR) imaging, greater LV dyssynchrony determined by CMR predicted adverse cardiovascular outcome in women but not in men.<sup>27</sup>

It is known that microvascular disease without significant epicardial coronary arteries lesions is more frequent in women; the fibrosis extension, in addition to the presence of ischemia, could be a possible explanation for the occurrence of more dyssynchrony in female patients, as we found in our cases.

In addition, differences in LVEF, volumes and dyssynchrony indices according to sex should be considered and strict comparison between male and female patients is not possible. Anyway, the results of the comparison between rest and stress dyssynchrony indices in the same sex patients can be hypothesis-generating regarding the role of mechanical dyssynchrony in the diagnosis and risk stratification of patients with chest pain and normal epicardial coronary arteries.

Nevertheless, this topic remains controversial. For instance, AlJaroudi et al. studied two groups of patients with normal LVEF and no fixed perfusion defects: one with reversible perfusion defects involving > 10% of the LV myocardium and the other with normal perfusion images. They found that the presence of even a large reversible perfusion defect does not alter the indices of mechanical dyssynchrony by phase analysis.<sup>28</sup> This was consistent with the work of Zhou et al.<sup>29</sup>

Our results, however, were different: in a previous work,<sup>30</sup> we found evidence of dyssynchrony in patients with stress-induced ischemia, mainly in those with larger ischemic perfusion defects. Furthermore, there are other published works that show similar results to ours. For instance, Chen et al,<sup>31</sup> using dipyridamole stress-rest thallium-201 gated MPI, found that in patients with ischemia, LV dyssynchrony was significantly greater during stress than during rest, but not in normal and scarred. They concluded that different post-stress dyssynchrony patterns between ischemic, scarred, and normal myocardium may aid the diagnosis of CAD.

AlJaroudi et al. studied 489 consecutive patients with ischemic cardiomyopathy and LVEF < 35% using rest/stress rubidium-82 gated PET and found that an increase of LV mechanical dyssynchrony during peak stress as compared to rest was an independent predictor of all-cause mortality. The authors consider that the fact that patients with an increase of LV mechanical dyssynchrony at stress had more ischemia on perfusion imaging would suggest that this could be an ischemia-driven phenomenon such as transient ischemic dilation.<sup>32</sup>

Potential factors that may affect dyssynchrony indices when processed from stress compared to rest gated images include: tracer dose, counts, type of stress test (pharmacologic versus exercise), temporal

resolution, timing of image acquisition post tracer injection, change in hemodynamics, LVEF, and ischemia. In our study, both stress and rest gated images were performed with the same tracer dose, the stress test was performed using physical exercise in all cases, and both acquisitions were made at 30 minutes. LVEF was normal. Therefore, in our case, the stress-induced ischemia can be an explanation for the increase of mechanical dyssynchrony with stress.

It is important to point out that as <sup>99m</sup>Tc-sestamibi or tetrofosmin gated-SPECT MPI images are usually acquired about 1 h after injection, they represent post-stress function in real time, which is close to resting function. As <sup>201</sup>Thallium gated-SPECT MPI images are acquired close to peak stress (within 5-10 minutes of injection), they allow investigating stress-induced changes in LV function and dyssynchrony. However, using <sup>99m</sup>Technetium-labeled compounds, if acquisitions are performed earlier than 1 hour post-stress, evidence of stress-induced dyssynchrony has been previously reported.<sup>8,9</sup>

## LIMITATION

This is a cross-sectional study and to better determine the clinical significance of the intraventricular synchrony findings, a follow-up study is required.

## CONCLUSION

Higher left ventricular volumes in females and degree of dyssynchrony are associated with inducible ischemia on stress testing in a gated-SPECT MPI in patients with chest pain and normal epicardial coronary arteries. Stress-induced ischemia increases the degree of intraventricular dyssynchrony.

## NEW KNOWLEDGE GAINED

Stress-induced ischemia increases the degree of intraventricular dyssynchrony in patients with chest pain and normal coronary arteries. The presence of fibrosis could enhance this behavior, mainly in females. However, further investigation is required.

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## Disclosure

*There are no conflicts of interest to disclose.*

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