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# Prognostic value of two-dimensional speckle-tracking echocardiography in patients with suspected ischemic heart disease

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**Competing interests**
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**Abbreviations**
**AMI:** acute myocardial infarction
**GLS:** global longitudinal strain
**LVEF:** left ventricular ejection fraction.
**MACE:** major adverse cardiac events
**ST-2D:** two-dimensional speckle-tracking echocardiography

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## ABSTRACT

*Introduction:* Two-dimensional speckle-tracking echocardiography has emerged as a novel method for the quantitative evaluation of myocardial function and it has been correlated with the presence of coronary artery disease.
*Objectives:* To determine the prognostic value of myocardial strain by two-dimensional speckle-tracking echocardiography in the evolution of patients with suspected ischemic heart disease.
*Method:* An analytical prospective longitudinal study was carried out with 51 patients, who underwent global longitudinal strain assessment by two-dimensional speckle-tracking echocardiography, and coronary angiography at CIMEQ between 2016 and 2018. Major cardiac adverse events (myocardial infarction, cardiac and non-cardiac cause of death, cerebrovascular disease, and need for new revascularization) were followed.
*Results:* The 70.6% of patients were male, the 81.4% were older than 50 years old, and the 81.4% were smokers. The 65.0% of patients had significant coronary artery disease and the 55.0% underwent myocardial revascularization. There were four deaths (7.8%) and one non-fatal myocardial infarction (2.0%). Patients with global longitudinal strain ≤ -15% (in absolute or modular values) had a higher frequency of major adverse cardiovascular events (p=0.02).
*Conclusions:* Global longitudinal strain by two-dimensional speckle-tracking echocardiography could not predict the presence of coronary artery disease, but it did predict major adverse cardiovascular events in patients with significant coronary artery disease.
*Keywords:* Speckle-tracking, Myocardial strain, Major adverse cardiac events, Ischemic heart disease

## *Valor pronóstico del speckle-tracking bidimensional en pacientes con sospecha de cardiopatía isquémica*

## RESUMEN

*Introducción: El estudio ecocardiográfico mediante speckle-tracking ha emergido como un novedoso método para la evaluación cuantitativa de la función miocárdica y se ha correlacionado con la presencia de enfermedad coronaria.*
*Objetivo: Determinar el valor pronóstico de la deformación miocárdica (strain)*

**Contribución de los autores**
AYRN, APB, RAA: Conception and design of the research; collection, analysis and interpretation of data, and drafting of the manuscript.
KRL, IMRF: Obtaining, analyzing, interpreting data, and assisting in the drafting of the manuscript.
JZG: Conception and design of the research, and assistance in writing the manuscript.
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*por speckle-tracking bidimensional en la evolución de pacientes con sospecha de cardiopatía isquémica.*
*Método: Estudio longitudinal prospectivo analítico con 51 pacientes a los que se realizó ecocardiograma con evaluación de la deformación (strain) longitudinal global por speckle-tracking bidimensional y coronariografía en el CIMEQ entre 2016 y 2018. Se siguieron los eventos cardíacos graves (infarto de miocardio, muerte cardíaca y por otras causas, enfermedad cerebrovascular y necesidad de nueva revascularización).*
*Resultados: El 70,6% de los enfermos resultaron ser del sexo masculino, el 81,4% mayores de 50 años y 81,4%, fumadores. El 65,0% tenía enfermedad coronaria significativa y 55,0% de los casos fueron revascularizados. Se registraron 4 muertes (7,8%) y un infarto no fatal (2,0%). Los pacientes con deformación longitudinal global ≤ -15% (en valores absolutos) tuvieron mayor frecuencia de eventos cardíacos graves (p=0,02).*
*Conclusiones: La deformación longitudinal global medida por speckle-tracking bidimensional no pudo predecir la presencia de enfermedad coronaria, pero sí los eventos cardiovasculares graves en los enfermos con enfermedad coronaria significativa.*
*Palabras clave: Speckle-tracking, deformación miocárdica, eventos cardíacos graves, cardiopatía isquémica*

## INTRODUCTION

Speckle-tracking echocardiography is a novel emerging diagnostic tool that allows for quantitative evaluation of global and regional myocardial function. Independently from the angle of insonation and from cardiac translational movements, speckle-tracking is more reproducible than tissue Doppler and other techniques that have assessed myocardial strain[1]. Both, extension and application of myocardial strain by two-dimensional speckle-tracking echocardiography (2D-ST) have been limited since initial softwares were time-consuming; however, criteria for its correct implementation have been standardized and conceptualized[2].

A number of publications have addressed 2D-ST for assessment of left ventricular function, referring to its normal values in different populations and its usefulness in a wide range of cardiac conditions, specifically ischemic heart disease[3], which has been the leading cause of morbidity and mortality in the world in the last 15 years, according to reports from the World Health Organization (9.4 million deaths in 2016)[4].

Official reports from 2017[5] indicate that in Cuba, 64.9% of deaths due to heart disease are caused by ischemic disease, of which 45.3% are related to acute myocardial infarction (AMI). Mortality from this cause is higher in older patients. It is therefore important to use simple, noninvasive methods to aid in the selection and prognosis of candidates for coronary angiography and invasive therapeutic procedures[6,7].

Several studies have demonstrated that 2D-ST at rest predicts the presence of left main and three-vessel coronary artery disease in patients with high-risk ischemic heart disease[8]; it is uncertain whether radial and circumferential strain can predict the presence, extent and location of significant coronary artery disease[9,10]. Amundsen *et al.*[11] have promoted 2D-ST for clinical use as it provides accurate measurements of regional myocardial strain, making it a potential tool for the assessment of regional myocardial function at the patient's bedside.

The predictive value of this method in assessing ventricular function has also been studied, especially in AMI and chronic coronary artery disease[12,13]. Previous studies regarding the application of 2D-ST have not been published in Cuba. Therefore, a question arises: Would it be possible to predict survival free of major adverse cardiac events (MACE) by assessing myocardial strain measured by 2D-ST in patients with suspected ischemic heart disease? Our research aims to determine the prognostic value of this variable in the clinical course of patients with suspected ischemic heart disease and thus answer the above question.

## METHOD

A prospective longitudinal analytical study was con-

ducted at the *Centro de Investigaciones Médico Quirúrgicas* (CIMEQ) in Havana, Cuba, between January 2016 and January 2018. The study population consisted of 721 patients who attended the specialized consultation for the first time with a clinical diagnosis of ischemic heart disease and an indication for coronary angiography. The sample consisted of 51 patients, after applying inclusion and exclusion criteria.

### Inclusion criteria

Patients over 18 years of age, who signed the informed consent, with an optimal acoustic window for 2D-ST echocardiographic assessment, were included.

### Exclusion criteria

- Clinical: Patients with cancer diseases, severe valvular heart disease, history of myocardial infarction, previous percutaneous coronary intervention or cardiac surgery, or both, and severe myocardial contractility disorder, systolic dysfunction, expressed by left ventricular ejection fraction (LVEF) <50%, atrial fibrillation, frequent premature ventricular contractions or other cardiac rhythm disorders.
- Echocardiographic: When 2D-ST tracking was inadequate in more than 3 segments.
- Related to follow-up: Patients who could not be followed-up for at least one year (as scheduled).

### Echocardiogram

Echocardiogram-related variables included M-mode examination (end-diastolic/end-systolic interventricular septal thickness, posterior wall thickness and left ventricular chamber diameter), in two-dimensional mode: LVEF (Simpson's biplane method), transmitral Doppler filling pattern (E/A waves and E/A ratio) and Doppler of the septal mitral annulus (s', e' wave velocity and E/e' ratio); as well as those related to the study of myocardial strain by 2D-ST: global longitudinal and segmental strain, and global circumferential strain. Normal values were taken into account according to the American Society of Cardiology and the European Association of Cardiac Imaging guidelines for cardiac chamber quantification in adults[14].

Patients were imaged in the left lateral decubitus position for initial assessment, after checking for normal heart rate and blood pressure. Data were acquired with a commercial EPIQ7 Ultrasound System (Philips Medical Systems) equipped with a 2.5 MHz probe. Two-dimensional gray scale images were approached from apical views: (four-chamber, two-chamber and long-axis views) and parasternal views (long-axis and short-axis views at the mitral valve, papillary muscles and apex). Three consecutive cardiac cycles were obtained during end-expiratory breath holding. Special care was taken to obtain correct apical and parasternal images, with the use of standard anatomical landmarks. All images were obtained at the same frame rate (50-80 frames/second). The analysis of the 2D-ST images –to determine global and segmental longitudinal strain– was performed using the Q Lab application, provided by the equipment manufacturer, with the use of apical two-, three- and four-chamber views. The software automatically detects the endocardial and epicardial borders, as well as all 17 segments related to the perfusion territory of the epicardial arteries for the operator to verify, edit –if necessary– and confirm, in order to generate the strain values, expressed in segmental and global percentages, which are displayed in bull's eye (polar map) diagram.

### Other variables

Additionally, variables related to angiographic evaluation were considered: extent of coronary artery disease, coronary arteries involved, degree of stenosis, presence of severe coronary artery disease, and coronary arterial dominance; as well as total follow-up time, type of treatment and the occurrence of MACE (death of cardiac origin or of any cause, non-fatal AMI and need for new coronary revascularization, alone or in combination), which were considered primary or main objectives during follow-up, according to the criteria of a large number of previous studies[15].

### Follow-up

Patients were followed up for a mean duration of one year, with variations depending on the date of enrollment, ranging from 124 to 917 days, with a mean of 608 days.

### Data collection

All relevant information on the 51 sample participants was documented on a chart based on their medical history, initial evaluation and follow-up appointments, as well as echocardiographic reports with a study of myocardial strain, coronary angiography and percutaneous coronary intervention, in case of having undergone such treatments. Control variables included were: age, sex, dyslipidemia, hy-

pertension, smoking, diabetes mellitus, and initial diagnosis leading to medical consultation.

### Statistical processing

Statistical analysis in the SPSS version 20.0 application was performed after obtaining a database. Measures of central tendency, frequency distribution, $\chi^2$, and the mean difference test were used. A Kaplan-Meier curve and the log-rank test (Mantel-Cox) were employed for survival analysis. Statistical significance was considered for $\alpha<0.05$.

### Ethics

Our study complied with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Informed (verbal and written) consent was obtained from all participants after being notified of their inclusion in the investigation, advantages of the tests (importance and usefulness) as well as objectives, risks and possible benefits of the research. In addition, they were informed of their right to opt out and withdraw their consent at any time without exposure to limitations to their medical care or other retaliation.

Specialized and trained medical personnel were in charge of patient care and evaluation. Patients' safety was respected throughout the research and their data confidentiality was guaranteed.

The research project was approved by the CIMEQ scientific board and ethics committee.

## RESULTS

Thorough observation of the clinical characteristics of the 51 patients selected for the study evidenced a predominance of the male sex (70.6%) and a mean age close to 60 years. There was a high incidence of all risk factors. The most frequent was hypertension (82.4%), followed by age over 50 years (81.4%); and stable angina (66.7%) was the clinical diagnosis prior to coronary angiography in more than half of the patients (**Table 1**).

A noteworthy fact is that the left anterior descending artery was the most frequently involved in terms of the site of injury in the left main coronary artery especially in the case of severe injuries (49%) (**Table 2**).

A 62.7% (32/51) of the individuals had coronary artery disease with significant lesions (**Table 3**). Multivessel disease predominated and right coronary artery dominance was present in a 92.2% of patients. Echocardiographic variables for the assessment of left ventricular systolic/diastolic function

**Table 1.** Baseline clinical characteristics of the patients.

| Characteristic | Nº | % |
|---|---|---|
| **Age (years, mean ± SD)** | 59.9 ± 9.4 | |
| **Male sex** | 36 | 70.6 |
| **Hypertension** | 42 | 82.4 |
| **Diabetes mellitus** | 12 | 23.5 |
| **Smoking** | 23 | 45.1 |
| **Dyslipidemia** | 17 | 33.3 |
| **Obesity** | 8 | 15.7 |
| **Over 50 years of age** | 41 | 81.4 |
| **Initial diagnosis** | | |
| NSTEACS | 17 | 33.3 |
| Stable angina | 36 | 66.7 |
| **Total** | 51 | 100.0 |

NSTEACS, non-ST-segment elevation acute coronary syndrome; SD, standard deviation

**Table 2.** Location and severity of lesions in the coronary artery tree.

| Artery | Severity of the coronary lesion | | | |
|---|---|---|---|---|
| | No lesion | Not significant (1-49%) | Significant (50-69%) | Critical (70% or more) |
| Right coronary artery | 30 (58.8) | 0 (0.0) | 2 (3.9) | 19 (37.3) |
| LMCA | 42 (82.4) | 2 (3.9) | 3 (5.9) | 4 (7.8) |
| LADA | 22 (43.1) | 2 (3.9) | 2 (3.9) | 25 (49.0) |
| Circumflex artery | 29 (56.9) | 1 (2.0) | 2 (3.9) | 19 (37.3) |

Values express n (%).
LADA, left anterior descending artery; LMCA, left main coronary artery

showed no significant differences in terms of presence or absence of significant coronary artery disease. We must highlight the fact that the patients selected for our investigation had a normal LVEF.

Global longitudinal strain assessed by 2D-ST was likewise unrelated to the extent of coronary artery disease (**Table 4**). However, better mean values were obtained among patients without significant coronary lesions (-22.1±3.6 vs. -20.0± 3.2; p=0.035). The same behavior presented this parameter when analyzed by 2-chamber (-23.0±4.1 vs. -19.7±4.5; p=0.008), 4-chamber (-21.6±3.6 vs. -20.7±3.7; p= 0.381); and 3-chamber (-22.2±4.8 vs. -19.4± 3.1; p=0.016) views]. No relevant results were obtained after individually comparing strain of each left ventricular segment between patients with and without coronary artery disease (**Table 5**).

A total 64.9% of patients underwent —either percutaneous (25.5%) or surgical (29.4%)— myocardial revascularization for ischemic heart disease. The remaining patients, mostly those without significant lesions, received optimal medical treatment. **Table 6** shows high coverage with the groups of platelet aggregation inhibitors, HMG-CoA (3-hydroxy-3-methyl-glutaryl coenzyme A) reductase inhibitors (statins), beta-blockers and angiotensin-converting enzyme inhibitors, but none showed statistical association with MACE.

Five MACE, 1 non-fatal AMI (2.0%) and 4 deaths (7.8%) were found during follow-up. Such events were more frequent in hypertensive patients and in those older than 50 years, without reaching a significant statistical difference (**Table 7**). Nor was a statistical association demonstrated when relating the values of global longitudinal strain obtained in the initial echocardiographic evaluation with MACE (**Table 8**).

Patients treated with percutaneous coronary intervention had a more satisfactory outcome when the (modular or absolute) GLS value was ≥ -20%, as no MACE occurred in this group. Patients who underwent coronary artery bypass graft and optimal medical treatment, however, fared better when the GLS was between -1 and -19.9%, since all had a MACE-free clinical course. Results, however, are not statistically significant.

Lastly, the analysis of MACE-free survival curve according to the GLS values recommended by the guidelines, with cut-off value -20 shows a high sur-

**Table 3.** Parameters of ventricular function and coronary artery disease.

| Parameters | Significant coronary lesions | | p |
|---|---|---|---|
| | No (n=19) | Yes (n=32) | |
| IVS diastole (mm) | 10.8 ± 2.5 | 11.3 ± 1.8 | 0.415 |
| IVS systole (mm) | 15.6 ± 2.9 | 15.1 ± 2.4 | 0.961 |
| PW diastole (mm) | 10.3 ± 1.3 | 11.3 ± 2.4 | 0.075 |
| PW systole (mm) | 15.7 ± 2.2 | 16.9 ± 3.6 | 0.248 |
| LV diastole (mm) | 45.8 ± 4.9 | 45.8 ± 6.4 | 0.998 |
| LV systole (mm) | 29.3 ± 5.2 | 30.5 ± 7.9 | 0.537 |
| EDV (ml) | 88.5 ± 27.9 | 99.9 ± 36.0 | 0.552 |
| ESV (ml) | 37.0 ± 14.4 | 40.1 ± 20.1 | 0.773 |
| LVEF (Simpson. %) | 55.5 ± 7.5 | 61.6 ± 7.5 | 0.183 |
| SF (%) | 34.9 ± 7.4 | 34.8 ± 8.2 | 0.878 |
| EDV (ml) | 83.1 ± 32.8 | 93.9 ± 23.9 | 0.458 |
| ESV (ml) | 30.8 ± 11.8 | 36.4 ± 11.4 | 0.125 |
| LVEF (Teich, %) | 62.6 ± 8.3 | 60.7 ± 6.5 | 0.371 |
| E wave (cm/s) | 72.7 ± 13.5 | 82.1 ± 19.1 | 0.127 |
| A wave (cm/s) | 72.2 ± 14.9 | 80.6 ± 20.3 | 0.157 |
| E/A ratio | 1.0 ± 0.3 | 1.1 ± 0.5 | 0.594 |
| Wave e' (cm/s) | 10.2 ± 3.6 | 9.6 ± 4.4 | 0.468 |
| Wave s' (cm/s) | 6.7 ± 1.5 | 7.2 ± 2.4 | 0.265 |
| E/e' ratio | 8.1 ± 3.7 | 9.7 ± 4.0 | 0.650 |

Values are expressed as mean ± standard deviation.
EDV, end-diastolic volume; ESV, end-systolic volume; IVS, interventricular septum; LV, left ventricle; LVEF, left ventricular ejection fraction; PW, posterior wall, SF, shortening fraction.

**Table 4.** Extensión de la enfermedad coronaria y deformación longitudinal global.

| Extent of disease | Global longitudinal strain | | Total |
|---|---|---|---|
| | -1 to -19.9 | -20 or less | |
| 1 vessel | 2 (50.0) | 2 (50.0) | 4 (7.8) |
| 2 vessels | 1 (20.0) | 4 (80.0) | 5 (9.8) |
| 3 vessels | 14 (58.3) | 10 (41.7) | 24 (47.1) |
| Non-significant lesions | 6 (33.3) | 12 (66.7) | 18 (35.3) |

p=0.26
Values express n (%)

vival rate for all GLS values, without establishing a difference between the groups created by the cut-off value (**Figure**). However, MACE (p=0.02) were much more frequent in patients with global longitudinal strain ≤ -15% (in modular or absolute values).

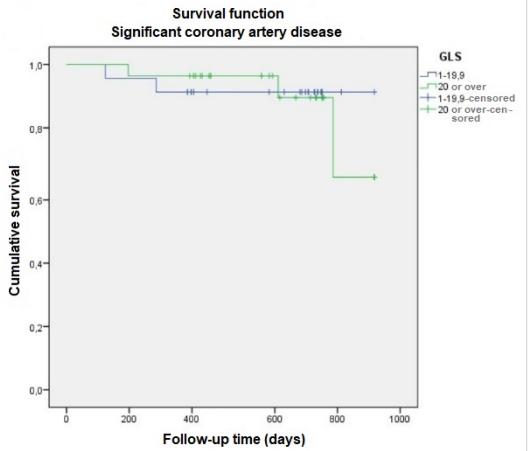


**Figure.** Kaplan-Meier survival curve according to global longitudinal strain (GLS). The test of equality of survival distribution for different GLS values (log Mantel-Cox ranges) shows that, regardless of the cutoff value, outcomes were similar, with no significant difference ($\chi^2$= 0.030; p=0.86).

**Table 5.** Global and segmental longitudinal strain according to the presence or absence of significant coronary lesions.

| LST variables | Significant coronary lesions | | *p* |
|---|---|---|---|
| | No (n=19) | Yes (n=32) | |
| **Global** | | | |
| GLS | -22.1 ± 3.6 | -20.0 ± 3.2 | 0.035 |
| GLS 2C | -23.0 ± 4.1 | -19.7 ± 4.5 | 0.008 |
| GLS 4C | -21.6 ± 3.6 | -20.7 ± 3.7 | 0.381 |
| GLS 3C | -22.2 ± 4.8 | -19.4 ± 3.1 | 0.016 |
| **Basal segments** | | | |
| Anterior septal | -18.3 ± 3.9 | -15.3 ± 4.7 | 0.019 |
| Anterior | -20.7 ± 4.6 | -19.1 ± 4.4 | 0.229 |
| Anterior lateral | -22.1 ± 3.6 | -19.6 ± 5.2 | 0.059 |
| Inferior septal | -15.9 ± 3.5 | -14.7 ± 2.9 | 0.153 |
| Inferior | -17.2 ± 4.9 | -15.3 ± 3.3 | 0.129 |
| Inferior lateral | -18.3 ± 4.9 | -15.4 ± 4.5 | 0.015 |
| **Medial segments** | | | |
| Anterior septal | -19.7 ± 5.9 | -16.6 ± 4.8 | 0.040 |
| Anterior | -20.4 ± 5.1 | -17.8 ± 4.8 | 0.070 |
| Anterior lateral | -19.9 ± 4.7 | -19.4 ± 5.3 | 0.703 |
| Inferior septal | -17.0 ± 5.1 | -17.3 ± 5.3 | 0.862 |
| Inferior | -21.5 ± 5.9 | -19.1 ± 6.0 | 0.164 |
| Inferior lateral | -23.4 ± 7.5 | -21.5 ± 5.3 | 0.271 |
| **Apical segments** | | | |
| Septal | -29.1 ± 5.4 | -28.4 ± 5.9 | 0.632 |
| Anterior | -25.5 ± 6.3 | -22.9 ± 5.5 | 0.116 |
| Inferior | -27.1 ± 4.5 | -24.4 ± 5.4 | 0.059 |
| Lateral | -22.1 ± 4.8 | -21.2 ± 4.1 | 0.478 |
| **Apex** | -25.3 ± 4.4 | -23.3 ± 4.1 | 0.097 |

Values are expressed as mean ± standard deviation.
2C, 2 chambers; 3C, 3 chambers; 4C, 4 chambers; GLS, global longitudinal strain; LST, speckle-tracking longitudinal

## DISCUSSION

### Characteristics of the studied patients

The study —performed in patients with suspected ischemic heart disease— showed a predominance of males and the mean age was around 60 years. Our results paralleled others published by the hemodynamics service of the center where the research was carried out[16], other institutions in Cuba[17-19] and in the world[20], both with respect to sex and age of the patients. A high frequency of risk factors was found among those with significant coronary lesions. Hypertension was the most frequent, which coincides with other Cuban reports on ischemic heart disease[21,22].

Three quarters of all participants with significant lesions had three-vessel disease. Reports on coronary angiographic findings from several published series, including one by the authors of this research, yielded similar results[23,24].

### Prognostic value of two-dimensional speckle-tracking

All GLS values were lower in patients with significant coronary artery disease, which coincides with several published studies comparing this variable, at rest, between patients with and without significant coronary artery disease[25,26]. Biering-Sørensen *et al.*[27] found that, in patients with suspected stable angina pectoris, GLS was significantly lower in patients with

**Table 6.** Major adverse cardiac events during follow-up, according to drugs used.

| Drugs (n=51) | Overall frequency | Patients without MACE* | p |
|---|---|---|---|
| Acetylsalicylic acid (ASA) | 32 (62.7) | 28 (87.5) | 0.40 |
| Clopidogrel | 27 (52.9) | 23 (95.8) | 0.20 |
| Statins | 31 (60.8) | 28 (90.3) | 0.96 |
| Beta-blockers (BB) | 16 (31.4) | 14 (87.5) | 0.66 |
| Nitrates | 19 (37.3) | 15 (78.9) | 0.04 |
| ACE/ARBs | 14 (27.5) | 11 (78.6) | 0.09 |
| Diuretics | 11 (21.6) | 9 (81.8) | 0.29 |
| Calcium-channel blockers | 8 (15.7) | 6 (75.0) | 0.12 |
| Alpha-blockers | 2 (3.9) | 1 (50.0) | 0.05 |
| Insulin | 2 (3.9) | 1 (50.0) | 0.05 |
| ASA/Clopidogrel/BB/Statins | 13 (25.5) | 12 (92.3) | 0.70 |

Values express n (%).
* Percentages calculated based on the overall frequency of drug use.
ACE, angiotensin-converting enzyme inhibitors; MACE, major adverse cardiac events; ARBs, Angiotensin II receptor type AT1 blockers.

**Table 7.** Major adverse cardiac events (MACE) during follow-up, according to the presence of cardiovascular risk factors.

| Risk factors (n=51) | Overall frequency | Patients with MACE* | p |
|---|---|---|---|
| Dyslipidemia | 17 (33.3) | 1 (5.9) | 0.45 |
| Smoking | 23 (45.1) | 3 (13.0) | 0.48 |
| Hypertension | 42 (82.4) | 5 (11.9) | 0.27 |
| Diabetes mellitus | 12 (23.5) | 1 (8.3) | 0.84 |
| Obesity | 8 (15.7) | 0 (0.0) | 0.50 |
| Male sex | 36 (70.6) | 4 (11.1) | 0.62 |
| Age over 50 years | 41 (81.5) | 5 (12.2) | 0.25 |

Values express n (%).
* Percentages calculated based on the frequency of each risk factor.

**Table 8.** Major adverse cardiac events according to global longitudinal strain.

| MACE | Global longitudinal strain | | Total | p |
|---|---|---|---|---|
| | -1 to -19.9% (n=23) | -20% or less (n=28) | | |
| **No MACE** | 21 (91.3) | 25 (89.3) | 46 (90.2) | |
| **MACE** | **2 (8.7)** | **3 (10.7)** | **5 (9.8)** | 0.82 |
| Death | 2 (8.7) | 2 (7.1) | 4 (7.8) | 0.83 |
| Acute myocardial infarction | 0 (0.0) | 1 (3.6) | 1 (2.0) | 0.36 |
| Cerebrovascular disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| New TLR | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |

Values express n (%).
MACE, major adverse cardiac events; TLR, target-lesion revascularization.

coronary artery disease compared to those without it (-17.1±2.5% vs. -18.8±2.6%; p<0.001). On the other hand, Choi *et al.*[28] propose its usefulness for predicting left main/three vessel coronary artery disease, where —according to the area under the curve— -17.9% could be used to discriminate severe coronary artery disease with a 79% sensitivity and specificity; in contrast to our findings, when patients are divided according to the number of significantly diseased arteries.

Billehaug *et al.*[29] in a review of 16 studies, state that GLS at rest is not sensitive enough to detect regional myocardial disease, thus its diagnostic accuracy in predicting significant coronary artery disease in patients with stable angina or acute coronary syndrome may be modest. In contrast, Bakhoum *et al.*[30] studied longitudinal and circumferential strain in patients with suspected stable coronary artery disease to predict the presence, extent and location of obstruction, and their results were significantly lower in patients with left main/three vessel coronary artery disease than in those with normal coronary arteries or one- or two-vessel disease.

Myocardial strain —when epicardial arteries and their possible irrigation zones were assessed— showed no statistically relevant differences, although they were lower in the segments corresponding to arteries with significant obstruction. This result is similar to that published by Billehaug *et al.*[29] and is explained by the fact that coronary anatomy is variable, so that assessing territorial function according to a specific vascular territory may not reflect the true arterial distribution; in addition, some areas may receive dual irrigation, including the development of collaterals.

Sarvari *et al.*[31] found differences in myocardial strain, by layers, between segments supplied by diseased or healthy arteries. Zhang *et al.*[32] have studied patients with non-ST segment elevation acute coronary syndrome using global and territorial myocardial strain —longitudinal and circumferential— of the three myocardial layers, according to the SYNTAX score.

Their results showed a sensitivity 72% and specificity 84% for endocardial GLS, using a cut-off value of -21.35%, and concluded that the use of 2D-ST by specific myocardial layers in this type of acute coronary syndrome is able to predict significant coronary lesions and endorsed it as a useful noninvasive method for decision-making in myocardial revascularization strategy.

Significant coronary stenosis has been shown to cause persistent impairment of longitudinal function at rest. This could be true in patients with significant stenosis, where intermittent ischemia causes subtle forms of myocardial stunning, which could be detected by strain measurements. Due to discrepancies on results, experts point out that it may be necessary to compare them with previous images of the same patient as it is usually done with electrocardiograms[12,33].

Regarding the prognostic value of 2D-ST in MACE-free survival in patients with suspected ischemic heart disease, our study only managed to establish a positive value in those with significant coronary artery disease. This issue has been addressed by multiple investigations in different areas of heart disease; 2D-ST left ventricular strain imaging have been shown to have additional prognostic value over conventional echocardiographic measurements in numerous studies with patients suffering from chronic[34,35] and acute[36] heart failure, AMI[37,38] and stable coronary artery disease[39].

It is important to note that the use of 2D-ST echocardiography, especially for assessment of global longitudinal strain, is highly valuable for detection of subclinical left ventricular dysfunction when LVEF is still normal[40]. Currently, the most common clinical value is the prediction of cardiotoxicity from cancer therapy[41]; but it has also been shown to be associated with unfavorable outcome of asymptomatic severe aortic stenosis[42] and hypertrophic cardiomyopathy with preserved LVEF[43]. Moreover, GLS impairment in populations with preserved LVEF and cardiovascular risk factors, including age[44], diabetes mellitus[45], hypertension[46], and obesity[47], may be an early marker of left ventricular systolic dysfunction.

Lauridsen *et al.*[48] have recently underlined the superiority of 2D-ST to LVEF in predicting the outcome of patients with left heart infective endocarditis. In this cohort, GLS > -15.4% stands out among the independent markers of mortality. In our series, patients with significant coronary artery disease with GLS > -15% had a worse outcome than the rest.

In a group of 829 patients with heart failure treated with resynchronization therapy, GLS was directly associated with a reduction in MACE and mortality during follow-up[49]. For their part, Yadlapati *et al.*[50] from the Bluhm Cardiovascular Institute in Chicago, USA, enrolled 122 patients referred for stress echocardiography for suspected coronary artery disease, who also underwent coronary angiography less than 3 months after stress echocardiography and were followed for 3.4 years for adverse cardiac events,

readmissions, and repeated cardiac examinations. Patients with a GLS <16.8% had a significant shortening in the time to onset of adverse effects, readmission, or new indication for ischemia testing.

Sikora-Frac and a group of researchers in Poland[51] evaluated 66 patients with coronary artery disease and LVEF ≥ 50% who were admitted for elective coronary angiography, and underwent percutaneous coronary intervention when coronary stenosis was greater than 70%, after evaluation by SYNTAX and EXTENT scores. Global longitudinal strain was used in addition to LVEF, peak myocardial velocity of the S' wave of left ventricular systole and Tei index calculated before and three months after the intervention in diabetic patients. These authors found that −prior to percutaneous coronary intervention− LVEF, GLS and Tei index were significantly worse in diabetic patients, and significantly improved after the intervention. Furthermore, an elevated SYNTAX score was associated with higher GLS. These results coincide with those of our investigation, where only ventricular function prior to coronary angiography was assessed and a relationship was found between GLS and the extent of coronary artery disease, although the SYNTAX score was not taken into account. In patients with extracardiac systemic diseases, such as sarcoidosis, without symptoms or signs of cardiovascular disease, even when LVEF is preserved, a GLS cut-off value ≤-13.6% was associated with a worse prognosis after a 57.1-month follow-up period[52]. Patients with chronic kidney disease have also been studied. Jahn *et al.*[53] in Germany assessed global longitudinal, circumferential and radial myocardial strain using 2D-ST in a group of 285 patients with advanced chronic kidney disease and compared them with 34 healthy individuals. They found that GLS was reduced in patients with the disease compared to healthy patients and demonstrated that GLS predicts death from any cause and from cardiovascular causes, independently of sex, age, presence or absence of diabetes, estimated glomerular filtration rate, and previous cardiovascular disease. Result which coincides with the report presented regarding MACE prediction.

A study from South Korea[54], on the other hand, included 160 patients with dilated cardiomyopathy in sinus rhythm and found a moderate to high correlation between ventricular function by GLS and LVEF during follow-up; while GLS was an independent predictor of negative left ventricular remodeling. Kaufmann *et al.*[55] report, −in their study of 193 patients with clinically stable heart failure of ischemic origin, with LVEF ≤ 50% and followed for an average of 34 months−, that MACE during follow-up were significantly associated with age, QRS width, heart failure functional class (NYHA), left atrial diameter, left ventricular end-diastolic and end-systolic volumes, LVEF, hemoglobin and B-type natriuretic peptide levels, diuretic treatment, absence of beta-blockers in treatment, worsening renal function and history of diabetes mellitus. Global longitudinal strain with a cut-off value of -9.4% was significantly associated with MACE and was therefore a predictor of hospitalization and heart failure decompensation. This result coincides with our research in finding the predictive value of GLS although only patients with LVEF ≥50% were included.

Similarly, in a meta-analysis of eight studies published by Al Saikhan *et al.*[56], two of them report an association between GLS and the occurrence of MACE and death from any cause; while in the remaining six, an association was found with combined MACE. In the pooled analysis, GLS predicted the presence of coronary artery disease, mortality and MACE, as well as the occurrence of heart failure, providing further evidence that GLS predicts total mortality and MACE in the general population; all of which is partially consistent with this research.

## STUDY LIMITATIONS

A limitation of this preliminary study was the small sample of patients. Assessment of myocardial strain was only performed in the initial evaluation; hence, its probable modification after myocardial revascularization procedure could not be analyzed. The sample included patients who were treated by both revascularization methods (percutaneous or surgical) and pharmacological methods, and with varying degrees of left main coronary artery involvement, who, in fact, have different outcomes.

## CONCLUSIONS

Global longitudinal strain by two-dimensional speckle-tracking echocardiography could not predict the presence of coronary artery disease in patients with suspected ischemic heart disease. However, it provided prognostic value on the occurrence of MACE during the clinical course of patients with significant coronary lesions.

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