Left Ventricular Longitudinal Global Strain to Predict Severe Coronary Disease in Patients with Precordial Pain Suggestive of Non-ST-Segment Elevation Acute Coronary Syndrome

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Abstract

Background: Diagnosing non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is not always straightforward. Left ventricular global longitudinal strain (LVGLS) is an echocardiographic method capable of detecting subclinical regional and global ventricular contractile dysfunction due to myocardial ischemia. The objectives of this study were to evaluate the efficacy of LVGLS in diagnosing severe coronary disease in patients with chest pain suggestive of NSTE-ACS and to assess the relationships between LVGLS reduction and ultrasensitive troponin T (UsTnT) elevation, electrocardiographic changes suggestive of ischemia, and the number of vessels with severe obstructions. Methods: This prospective, observational study evaluated hospitalized patients with chest pain of presumed coronary etiology. All patients underwent electrocardiography (ECG), UsTnT measurement, Doppler echocardiography, LVGLS measurement, and coronary angiography Coronary angiogram (CA) within 48 h of hospitalization. Results: A total of 75 patients with a mean age of 58 ± 17 years were included, of whom 84% (63 patients) were men. An LVGLS value of <−16.5, as determined by the Youden index proved to be useful for the detection of severe coronary obstructions (lesions >70%). The sensitivity, specificity, and positive and negative predictive values were 96%, 88%, 92%, and 92%, respectively. The number of coronary arteries involved had a direct relationship with the degree of LVGLS reduction (P < 0.001). Elevated UsTnT levels occurred more frequently in patients with reduced LVGLS than in those with normal LVGLS (83% vs. 17%, P < 0.0001). Abnormal strain was not associated with electrocardiographic changes suggestive of ischemia. Conclusions: LVGLS measurement in patients with presumed NSTE-ACS is efficient in predicting the presence of severe coronary disease. The number of coronary arteries involved has a direct relationship with the degree of LVGLS reduction. Abnormal strain is associated with UsTnT elevations but not with electrocardiographic changes suggestive of ischemia.

Keywords: Left ventricular global longitudinal strain, myocardial ischemia, non-ST-segment elevation acute coronary syndrome, ultrasensitive troponin T

Introduction

The diagnosis of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is based on clinical presentation, electrocardiographic changes, and cardiac enzyme curves. In many cases, the diagnosis is a challenge because the symptoms may be atypical, electrocardiogram (ECG) findings may be normal or nonspecific, and cardiac enzymes may not be elevated.[1] Approximately 30% of patients hospitalized with presumptive diagnosis of NSTE-ACS do not show evidence of significant angiographic lesions in the coronary angiogram (CA).[2] A noninvasive diagnostic method capable of more precisely discriminating those patients who will benefit from an early CA and coronary revascularization from those who do not require an invasive procedure would be welcomed.

Myocardial ischemia in patients with NSTE-ACS produces segmental wall motion abnormalities. The degree of ventricular dysfunction depends on the number of coronary arteries involved and the extent of coronary obstruction. Ultrasensitive troponin T (UsTnT) elevation is considered a marker of myocardial ischemia. LVGLS is an echocardiographic method capable of detecting subclinical regional and global ventricular contractile dysfunction due to myocardial ischemia. This technique has been shown to be relevant in patients with NSTE-ACS.[3] The purpose of this study was to evaluate the efficacy of LVGLS in predicting severe coronary disease in patients with chest pain suggestive of NSTE-ACS and to assess the relationships between LVGLS reduction and UsTnT elevation, electrocardiographic changes suggestive of ischemia, and the number of vessels with severe obstructions.

Methods

This prospective, observational study evaluated hospitalized patients with chest pain of presumed coronary etiology. All patients underwent electrocardiography (ECG), UsTnT measurement, Doppler echocardiography, LVGLS measurement, and coronary angiography (CA) within 48 h of hospitalization.

Results

A total of 75 patients with a mean age of 58 ± 17 years were included, of whom 84% (63 patients) were men. An LVGLS value of <−16.5, as determined by the Youden index, proved to be useful for the detection of severe coronary obstructions (lesions >70%). The sensitivity, specificity, and positive and negative predictive values were 96%, 88%, 92%, and 92%, respectively. The number of coronary arteries involved had a direct relationship with the degree of LVGLS reduction (P < 0.001). Elevated UsTnT levels occurred more frequently in patients with reduced LVGLS than in those with normal LVGLS (83% vs. 17%, P < 0.0001). Abnormal strain was not associated with electrocardiographic changes suggestive of ischemia.

Conclusions

LVGLS measurement in patients with presumed NSTE-ACS is efficient in predicting the presence of severe coronary disease. The number of coronary arteries involved has a direct relationship with the degree of LVGLS reduction. Abnormal strain is associated with UsTnT elevations but not with electrocardiographic changes suggestive of ischemia.
arteries affected, severity of the obstructions, and extent of the myocardial territory involved. Two-dimensional echocardiography with speckle tracking is a validated technique that measures the strain (deformation) of the left ventricular wall.[3-5] It allows more accurate evaluation of left ventricular segmental and global systolic function than the visual changes assessed with traditional echocardiographic methods.[6,7]

In patients hospitalized with precordial pain, it is conceivable that evaluation of left ventricular global longitudinal strain (LVGLS) may distinguish those with severe coronary obstructions who could benefit from an early CA (reduced LVGLS) from those who should undergo a noninvasive functional test (normal LVGLS).[8] Thus, the primary objective of this study was to determine the efficacy of LVGLS to identify severe obstructive coronary disease in patients hospitalized with presumed NSTE-ACS. The secondary objective was to analyze the relationships between LVGLS reduction and elevation of ultrasensitive troponin T (UsTnT), electrocardiographic changes suggestive of ischemia, and the number of vessels with severe lesions.

**METHODS**

**Population**

This prospective, observational study was conducted in a tertiary hospital between April 2016 and September 2018. Patients older than 18 years who were admitted to the coronary unit with a presumptive diagnosis of NSTE-ACS based on clinical presentation were enrolled. All patients were evaluated with ECG and UsTnT curves and underwent Doppler echocardiography at rest and LVGLS measurement with speckle tracking before undergoing a CA within 48 h of hospitalization. Patients were excluded if they had a history of previous coronary disease (clinical history of infarction or electrocardiographic evidence of old infarction, aortocoronary bypass, or percutaneous procedures), complete left bundle branch block, ECG with ST-segment elevation, ventricular arrhythmia, pacemaker rhythm, preexcitation, and atrial fibrillation with more than 100 beats per minute. Patients with any form of cardiomyopathy or severe valvular disease, with suboptimal acoustic window, or with severe comorbidities and a life expectancy of <1 year were also excluded. The protocol was approved by the Ethics Committee of the Sanatorium Allende, and the patients gave informed consent.

**Diagnostic methods**

ECG was performed at the time of admission and repeated at 3, 12, and 24 h or if any change in the symptoms occurred. The ECG View™ version 2.12.0 (Eccosur™ Buenos Aires, Argentina) digital system with 12 simultaneous derivations was used. The ECG criteria used to diagnose ST-segment changes suggestive of ischemia were based on the European guidelines for NSTE-ACS.[9]

UsTnT levels were measured at admission and after 3 h, and values that exceeded the 99th percentile of normality (14 ng/dL in our laboratory) were considered abnormal.

Transthoracic echocardiograms were performed with electrocardiographic control before CA. Vivid™ E9 and E9.5 (GE Vingmed, Horten, Norway) echocardiograms were used, and postprocessing was done with the GE EchoPac™ version 110 software. Images were obtained in the parasternal views in the long, short, and apical axes of 4, 3, and 2 cameras. Three consecutive cycles were recorded in each projection. Color Doppler images of the mitral, aortic, tricuspid, and pulmonary valves were taken, and flows with continuous and pulsed Doppler were obtained to determine the presence of valvular heart disease. Ejection fraction (EF) was calculated using the modified Simpson formula in 4 and 2 cameras at the end of systole and diastole with the automatic edge detection method.

The LVGLS was measured by the speckle tracking technique in 4, 3, and 2 apical chamber views, calculating a 16-segment model (6 segments in each view used) using the automated function imaging method.[9] The endocardial edge of the left ventricle was manually drawn, and the width of the region of interest was adjusted so that only the walls of the left ventricle were included. Deformation was monitored with the software automatically. The frame rate used was 72 ± 15 frames per second. For each segment, the maximum negative systolic value of strain representing the maximum contractility of this segment was measured. The values of each segment were averaged, obtaining the global longitudinal strain.[9] The value of the LVGLS considered within the normal limits for the software used was ≥17. The values were expressed in absolute numbers, clarifying that they indicated an increase or decrease in strain to avoid confusion since the shortening and elongation of the myocardial fibers are expressed in negative and positive values, respectively.[10] The echocardiographic images and LVGLS processing were performed by a single experienced sonographer who was unaware of the patients’ clinical information.

Diagnostic CA were carried out with a Siemens Artis One or a Phillips Allura FD10 angiographer (Omaha, NE, USA) using the Judkins technique within 48 h of the patient’s admission. The decision to revascularize and the method of revascularization, was left to the discretion of the treating cardiologist. A severe coronary lesion was defined as the presence of an obstruction >70% of 1 or more epicardial arteries or an obstruction >50% of the left main coronary artery. Image analysis was conducted by an experienced cardiologist who was unaware of the LVGLS outcome. The interobserver and intraobserver variability for this method is 0%–5% and 0%–1.3%.[11]

**Statistical analysis**

Continuous variables were expressed as mean ± standard deviation and were compared using Student’s *t*-test or the Mann–Whitney *U*-test, as appropriate. Categorical variables were expressed as percentages and compared using the Chi-square test or Fisher’s test, as appropriate. The prediction of severe coronary obstruction by LVGLS was evaluated.
by determining the area under the curve receiver operating characteristic that established the sensitivity and specificity through the different values of myocardial deformation. The relationship among 3 or more variables was assessed through analysis of variance, and that between 2 variables was assessed using Student’s t-test. A P < 0.05 was considered significant.

RESULTS
The baseline characteristics of 75 patients are given in Table 1. The echocardiographic assessment showed a mean EF of 60% and a mean LVGLS of −15 ± 3, which was normal in 32% and reduced in 68%. Cardiac catheterization showed that 33% of the patients did not have angiographically significant lesions. Of those with severe obstructions, 27% had lesions in 1 vessel, 24% had lesions in 2 vessels, and 16% had severe obstructions in 3 vessels. A total of 44 patients were revascularized. Aortocoronary bypass and percutaneous coronary intervention were performed in 4 (6%) and 40 patients (64%), respectively. Laboratory values and electrocardiographic, echocardiographic, and angiographic findings are also shown in Table 1.

Compared with patients without significant coronary lesions, those with severe obstructions in at least 1 vessel had a higher prevalence in male sex, were smokers, and had higher UsTnT level, lower EF, and lower LVGLS.

Compared with patients with normal LVGLS, those with decreased LVGLS showed no differences in the presence of traditional risk factors except for smoking, which was more prevalent in patients with altered strain [Table 2]. Abnormal LVGLS correlated directly with the number of vessels with severe lesions [Figure 1]. Elevated UsTnT levels occurred more frequently in patients with abnormal LVGLS than in those with normal LVGLS (17% vs. 83%, P<.0001). Abnormal strain had no association with electrocardiographic changes [Table 2].

An LVGLS value of ≤−16.5, as determined by the Youden index, proved to be useful for the detection of severe coronary obstruction (sensitivity, 96%; specificity, 88%; positive predictive value, 92%; negative predictive value, 92%). The area under the curve was 0.91. Abnormal UsTnT levels and electrocardiographic changes were less efficient in predicting the presence of severe lesions in the CA [Table 3].

DISCUSSION
The results of this study show that the measurement of LVGLS in patients admitted with presumed NSTE-ACS is efficient in distinguishing patients who have severe obstructive disease from those without significant lesions. The sensitivity, specificity, positive predictive value, and negative predictive value of LVGLS were excellent and superior to those provided by UsTnT elevation and electrocardiographic changes suggestive of ischemia. Furthermore, a direct relationship was found between LVGLS reduction and the number of coronary arteries with severe obstructions. Although reduced strain was associated with elevated UsTnT, it was not associated with electrocardiographic changes suggestive of ischemia.

| Table 1: Baseline characteristics (n=75) |
|----------------------------------------|
| VARIABLE                  | VALUE       |
| Age (years)              | 58±17       |
| Male                     | 63 (84)     |
| Risk factors             |             |
| Hypertension             | 51 (68)     |
| Diabetes                 | 19 (25)     |
| Dyslipidemia             | 28 (37)     |
| Renal insufficiency      | 8 (11)      |
| Smoker                   | 28 (37)     |
| Medication               |             |
| Antiplatelets            | 19 (25)     |
| Beta-blockers            | 18 (24)     |
| Statins                  | 20 (27)     |
| ACEI/ARB                 | 32 (43)     |
| Diuretics                | 5 (7)       |
| Others                   | 7 (11)      |
| ECG                      |             |
| Normal                   | 19 (25)     |
| ST depression            | 11 (15)     |
| Negative T waves         | 28 (37)     |
| Others                   | 17 (23)     |
| Doppler echocardiogram   |             |
| LV mass                  | 163.9±53    |
| EF                       | 60±11       |
| LVGLS strain             | −15±3       |
| Coronary angiogram       |             |
| No significant lesions   | 25 (33)     |
| One-vessel disease       | 20 (27)     |
| Two-vessel disease       | 18 (24)     |
| Three-vessel disease     | 12 (16)     |
| Angiogram <48 h          | 75 (100)    |
| Positive UsTnT           | 58 (77)     |
| Treatment                |             |
| Medical                  | 19 (30)     |
| PCI                      | 40 (64)     |
| Bypass                   | 4 (6)       |

Values are presented as mean±standard deviation or n (%). ACEI/ARB=Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, ECG=Electrocardiogram, EF=Ejection fraction, LV=Left ventricle, LVGLS=Left ventricular global longitudinal strain, PCI=Percutaneous coronary intervention, UsTnT=Ultrasensitive troponin T

Figure 1: Relationship between left ventricular global longitudinal strain and the number of vessels with severe disease
 assessing these changes with traditional echocardiographic methods.\(^3\) The reason is that the measurement of EF is based predominantly on the assessment of changes in ventricular volumes and that the visual evaluation of segmental wall motion abnormalities depends on myocardial thickening. Both parameters are insensitive markers of ischemia since the preserved circumferential function in the nonischemic midwall, and subepicardium opposes sufficient decrease in EF and inward motion.\(^{12,13}\) The LVGLS, however, measures actual deformation in the subendocardial myocardium, which is very susceptible to early ischemic changes and can discriminate patients with or without significant coronary disease.\(^{12,13}\)

The results of this work revealed that the LVGLS with a cutoff value of \(<-16.5\) is useful in discriminating patients with severe coronary disease, with both positive and negative predictive values of 92%. A meta-analysis of 10 studies that included 1385 patients revealed that the LVGLS measurement predicted moderate and severe coronary disease with a sensitivity of 74.4%, a specificity of 72.1%, and an area under the curve of 0.80.\(^{10}\) These values are lower than those observed in the present work, which has a sensitivity of 96%, specificity of 84%, and an area under the curve of 0.91. The discrepancy is likely due to differences in the populations studied and the criteria for defining significant coronary disease. The trials that were part of the meta-analysis evaluated patients with an intermediate pretest probability of significant coronary artery disease, including both patients with presumed NSTE-ACS and those with stable angina. Angiographically significant lesions were defined as moderate- and severe-degree (>50%) obstructions. Meanwhile, in the present study, the evaluated population had a high pretest probability because only patients with presumed NSTE-ACS were evaluated, excluding those with chronic symptoms. The other difference was that only severe obstructions (>70%) were considered angiographically significant, excluding moderate lesions (50%–70%).

The present study showed a direct relationship between the number of coronary arteries with severe lesions and the degree of LVGLS reduction, which implies that the extent of ischemic territory influences the degree of LVGLS reduction, consistent with the findings of previous studies.\(^{11,15}\) The observation that patients with elevated UsTnT levels more frequently had abnormal LVGLS than patients with normal cardiac enzyme levels corroborates this concept.

The lack of association between reduced LVGLS and electrocardiographic changes suggestive of ischemia in this work was not unexpected given that the specificity of repolarization abnormalities in diagnosing ischemia is low.\(^{16}\) Acute processes such as myocarditis and Takotsubo syndrome as well as chronic conditions such as arterial hypertension and valvulopathies can cause similar ECG repolarization abnormalities that may be indistinguishable from ischemic ones.

The false-positive results in patients with reduced LVGLS possibly occur in patients with conditions such as Takotsubo

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**Table 2: Differences between patients with normal strain and those with reduced strain**

| Characteristics        | Normal strain, \(n=24\) | Reduced strain, \(n=51\) | \(P\) |
|------------------------|--------------------------|--------------------------|------|
| Hypertension           | 14 (27)                  | 37 (73)                  | 0.21 |
| Diabetes               | 6 (32)                   | 13 (63)                  | 0.96 |
| Dyslipidemia           | 8 (29)                   | 20 (71)                  | 0.62 |
| CRI                    | 2 (25)                   | 6 (75)                   | 0.65 |
| Smoker                 | 5 (18)                   | 23 (82)                  | <0.05|
| Antiplatelets          | 4 (21)                   | 15 (79)                  | 0.23 |
| Beta-blockers          | 3 (17)                   | 15 (83)                  | 0.12 |
| Statins                | 6 (30)                   | 14 (70)                  | 0.90 |
| ACEI/ARB               | 11 (34)                  | 21 (66)                  | 0.70 |
| Diuretics              | 2 (40)                   | 3 (60)                   | 0.69 |
| Others                 | 2 (29)                   | 5 (71)                   | 0.73 |
| Coronary angiogram     |                          |                          |      |
| No coronary lesions    | 22 (88)                  | 3 (12)                   | <0.0001|
| One-vessel disease     | 2 (10)                   | 18 (90)                  | <0.05|
| Two-vessel disease     | 0 (0)                    | 18 (100)                 | <0.001|
| Left main disease      | 0 (0)                    | 12 (100)                 | <0.01|
| Positive UsTnT         | 10 (17)                  | 48 (83)                  | <0.0001|

Values are presented as \(n\) (%). ACEI/ARB=Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, CRI=Chronic renal insufficiency, ECG=Electrocardiogram, UsTnT=Ultrasensitive troponin T

**Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of left ventricular global longitudinal strain, ultrasensitive troponin T, and electrocardiogram changes for the diagnosis of severe coronary lesions**

|                     | Reduced strain (%) | Positive UsTnT (%) | Abnormal ECG (%) |
|---------------------|--------------------|--------------------|------------------|
| Sensitivity         | 96                 | 96                 | 78               |
| Specificity         | 88                 | 60                 | 32               |
| PPV                 | 92                 | 83                 | 70               |
| NPV                 | 92                 | 88                 | 42               |

ECG=Electrocardiogram, LVGLS=Left ventricular global longitudinal strain, NPV=Negative predictive value, PPV=Positive predictive value, UsTnT=Ultrasensitive troponin T

The available algorithms to stratify the cardiovascular risk of patients presenting with chest pain are tedious and imprecise, which explains why approximately 1/3 of cases undergoing cardiac catheterization show no evidence of significant lesions.\(^{10}\) A rapid and straightforward noninvasive diagnostic method to rule out severe coronary disease beyond the information provided by the clinical presentation, ECG changes, and enzymatic markers is needed.

LVGLS assessment is innocuous and can be performed in a few minutes without the need to subject patients to physical exercise. It can detect global and segmental wall motion abnormalities induced by ischemia more sensitively than
syndrome, myocarditis, and coronary spasms, in which CA is the only way to determine the differential diagnosis. Alternatively, false-negative results in patients with normal LVGLS may occur when acute ischemic events involve myocardial territories small enough not to induce segmental wall motion abnormalities or when collateral circulation limits the magnitude of ischemia.[10,13]

The clinical implications of this study are that LVGLS is a practical and novel diagnostic method that could be integrated with ECG and cardiac enzymes as part of routine evaluation in patients with chest pain. Unlike the UsTnT, which elevates 1–3 h after the onset of symptoms, thus delaying the confirmation of NSTE-ACS in many cases, the alteration of the LVGLS allows the immediate confirmation of ischemia because myocardial contractile dysfunction occurs only seconds after reduction of tissue perfusion.[17] This capability and its high positive predictive value make LVGLS an ideal tool for evaluating patients with chest pain in the emergency room and thus identifying those patients who will benefit from an early CA. Alternatively, the high negative predictive value of the LVGLS could reduce the number of unnecessary CA, which is expensive and not without risk. Until studies prove that it is safe to use a “negative strain” as a marker for patients who do not warrant CA and could undergo noninvasive functional testing, LVGLS should be considered a complementary method to existing risk stratification.

This study has some limitations. First, the number of patients included was not large enough to be categorical with respect to our conclusions. Second, although the LVGLS was performed before the CA, as per protocol, in many cases, it was performed after the chest pain had subsided. It would have been more advantageous to assess LVGLS at the time of arrival in the emergency room or shortly after when wall motion abnormalities induced by ischemia are more likely to be detected. Possibly, some of the false-negative results observed in this study occurred in patients with NSTE-ACS whose ischemia had subsided when the echocardiography was performed. Unfortunately, the relation between chest pain, electrocardiographic changes and echo by LVGLS was not recorded. Third, the LVGLS cannot be applied to all patients, as it may provide misleading information in patients with a history of coronary disease and those with preexisting wall motion abnormalities, as it may be unable to differentiate chronic wall motion abnormalities from those induced by acute ischemia. In the present study, we excluded patients with prior history of CAD minimizing the chance of including subjects with preexisting wall motion abnormalities. Even though we cannot exclude this possibility; if present it should be minimal given the normal baseline EF of the study population. Fourth, evaluating only the global longitudinal strain and not assessing the radial and circumferential strain could be considered a limitation. Longitudinal strain was the only one assessed because, as an indicator of ischemia, it has been shown to be more sensitive than the other strain types, which are currently not supported by cardiac imaging societies.[18] Fifth, the echocardiographic parietal motility index was not used because it is operator dependent, and we preferred to investigate a semiautomatic technique that has less interobserver variability. Finally, given the low number of patients included, we elected not to discriminate the coronaries involved, rather reporting only the number of arteries compromised.

**Conclusions**

The measurement of LVGLS in patients with presumed NSTE-ACS is efficient in predicting the presence of severe coronary disease. There is a direct relationship between the degree of LVGLS reduction and the number of coronary arteries involved. The strain was associated with elevations of UsTnT, but not with electrocardiographic changes suggestive of ischemia.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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