

Pathophysiology and Prognosis of Apical Longitudinal Strain During Dipyridamole Stress Echocardiography

Fisiopatología y pronóstico de la deformación longitudinal regional durante el eco estrés con dipiridamol

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ABSTRACT

Background: Regional apical longitudinal strain can corroborate the diagnosis of regional wall motion abnormalities on a quantitative basis, but data on long-term prognostic value are lacking.

Objectives: To evaluate the physiological correlate and the prognostic value of apical longitudinal strain versus wall motility during dipyridamole stress echocardiography.

Methods: Retrospective study, which included 150 patients referred for dipyridamole stress echocardiography. Apical longitudinal strain, anterior descending artery coronary reserve, and visual analysis of wall motility were evaluated. Patients were divided into two groups. Group 1: patients with normal apical longitudinal strain, and Group 2: abnormal strain. Follow-up was carried out for 36 ± 9.3 months. Major event was defined as: death, myocardial infarction, revascularization and hospitalization for cardiac causes.

Results: Eighty-seven patients (61.3%) in Group 1 and 55 (38.7%) patients in Group 2 were included (8 patients were excluded due to a suboptimal ultrasound window). There were no differences in apical longitudinal strain at rest between the groups. During the stress, Group 1 patients showed better visual wall motility and a higher coronary reserve ($p < 0.001$). The coronary reserve showed a linear correlation with the changes in the apical longitudinal strain (Pearson's correlation coefficient 0.89, $p < 0.0001$). At follow-up, there were 24 major events. Group 1 patients had better event-free survival ($p < 0.01$) and apical longitudinal strain proved to be a better independent event predictor than wall motion analysis ($p = 0.002$ vs $p = 0.1$) in logistic regression analysis.

Conclusions: Apical longitudinal strain has a very good correlation with physiological standards –coronary flow velocity reserve– and its association with long-term prognosis is better. Abnormal apical longitudinal strain during dipyridamole stress echocardiography predicted a worse outcome, regardless of visual wall motion analysis.

Key Words: Ventricular Function, Left - Echocardiography, Stress - Dipyridamole - Predictive Value of Tests

RESUMEN

Introducción: El *strain* longitudinal apical regional permite corroborar el diagnóstico de alteraciones regionales de la motilidad parietal sobre una base cuantitativa, pero faltan datos sobre su valor pronóstico a largo plazo.

Objetivos: Evaluar el correlato fisiológico y el valor pronóstico del *strain* longitudinal apical en el eco estrés con dipiridamol frente a la motilidad parietal.

Material y métodos: Estudio retrospectivo, que incluyó 150 pacientes remitidos para eco estrés con dipiridamol. Se evaluó el *strain* longitudinal apical, la reserva coronaria (RC) de la arteria descendente anterior y el análisis visual de la motilidad parietal. Los pacientes se dividieron en dos grupos. Grupo 1: pacientes con *strain* longitudinal apical normal y Grupo 2: con *strain* anormal. Se realizó seguimiento por $36 \pm 9,3$ meses. Evento mayor fue definido como: muerte, infarto de miocardio, revascularización e internación por causa cardíaca.

Resultados: Fueron incluidos en el análisis 142 pacientes (8 pacientes fueron excluidos por ventana ultrasónica subóptima), 87 (61,3%) en el Grupo 1 y 55 (38,7%) en el Grupo 2. No hubo diferencias en el *strain* longitudinal apical en reposo entre ambos grupos. Durante el apremio, los pacientes del Grupo 1 evidenciaron mejor motilidad parietal visual y una RC más alta ($p < 0,001$). La RC y los cambios del *strain* longitudinal apical presentaron una correlación positiva (coeficiente r de Pearson = 0,89, $p < 0,0001$).

En el seguimiento hubo 24 eventos mayores. Los pacientes del Grupo 1 tuvieron una mejor supervivencia libre de eventos ($p < 0,01$) y el *strain* longitudinal apical demostró ser un predictor independiente de evento, mejor que el análisis de motilidad parietal ($p = 0,002$ vs $p = 0,1$), en el análisis de regresión logística.

Conclusiones: El *strain* longitudinal apical tiene muy buena correlación con: la reserva de velocidad del flujo coronario y se asocia mejor con el pronóstico a largo plazo. El *strain* longitudinal apical anormal durante el eco dipiridamol predijo un peor resultado, independientemente del análisis visual de la motilidad parietal

Palabras clave: Función Ventricular Izquierda - Ecocardiografía de Estrés - Dipiridamol - Valor Predictivo de las Pruebas

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INTRODUCTION

Within the agents used for stress echocardiography, dipyridamole is one of the recommended drugs for the diagnosis and prognosis of coronary artery disease. It is not widely used in echocardiography laboratories due to lack of knowledge or for personal, geographical, financial or availability reasons, rather than for truly scientific criteria. Its use according to the state of the art, in high doses and short infusion time with the addition of atropine and/or hand grip, offers a level of diagnostic accuracy similar to dobutamine, with a three times lower rate of severe complications. (1-2) Subjectivity in the analysis of results and operator experience have always been the major limitations of stress echocardiography; therefore, quantitative techniques have been applied, such as measuring the anterior descending artery (ADA) coronary flow reserve (CFR) and myocardial strain with the speckle-tracking technique. (3)

Determination of CFR in the distal ADA has been performed in our laboratories since 1998 and is now spreading in many centers around the world due to its added prognostic value to motion wall analysis, and to increased study sensitivity in detecting epicardial coronary lesions with only a slight decrease in specificity, considering that its assessment includes comprehensive information on the coronary macrovascular tree and microvascular function. (2,4-6)

However, wall motion and CFR should not be considered as alternative but rather complementary and additional determinations during dipyridamole stress echocardiography.

Moreover, a better knowledge of myocardial anatomy and function has led to a more detailed understanding of the muscle strain mechanism. Longitudinal function analysis—which evaluates the subendocardial fibers, more susceptible to ischemia, using the speckle-tracking strain technique—has been shown to increase study sensitivity compared to visual analysis of wall thickening. (7) Therefore, in a third generation of tests, contractility, CFR and strain are simultaneously assessed since 2006 in all patients undergoing dipyridamole stress echocardiography.

This is a highly feasible pharmacological stress test, with short imaging time and minimal quality loss, because the patient is comfortable at rest to start training without excessive hyperventilation or tachycardia. We consider dipyridamole stress echocardiography to be the perfect match for direct CFR assessment and for the use of new techniques such as the speckle tracking approach.

Longitudinal strain assesses internal descending fibers highly dependent on subendocardial flow, and can be global or regional. When the behavior of the apical segments is considered, a comparison can be made with regional wall motion abnormalities and CFR on a fully quantitative basis.

Our previous studies showed the excellent correlation between apical longitudinal strain and CFR, but

demonstrating whether these parameters are able to better stratify patient prognosis than visual contractility analysis was still pending. (8)

OBJECTIVES

The purpose of this study was to evaluate the physiological correlate and the prognostic value of apical longitudinal strain versus wall motion during dipyridamole stress echocardiography.

METHODS

Population

It is a retrospective, observational, single-center study including 150 patients assessed with dipyridamole stress echocardiography at our center over a 2-year period (from January 2017 to January 2019).

Inclusion criteria was global and regional normal resting function. Only patients with previous infarction in a territory other than ADA or with a history of myocardial revascularization without wall motion disorders at rest were included.

Exclusion criteria included structural heart disease of different etiology (e.g., valve disease), complete left bundle branch block, atrial fibrillation, or inadequate ultrasound window.

All patients underwent dipyridamole stress echocardiography (0.84 mg/kg in 4 min), according to the protocol adopted in our laboratory since 1998. (7) Prior to the study, all patients signed an informed consent form for the test and data use for scientific purposes.

Stress echocardiography

Patients had to fast for at least 4 hours and be free of xanthine drugs and/or infusion intake 12 hours prior to the study. Intravenous infusion of dipyridamole was the stressor used. A Vivid E 9 or E95 (GE Healthcare) ultrasound system was used, with 5 MHz Matrix transducer and two-dimensional (2D) image acquisition at a rate of 60-70 frames/second. Evaluation of usual echocardiographic parameters was performed according to the American Society of Echocardiography guidelines.

Left ventricular ejection fraction (LVEF) was obtained automatically.

ADA was visualized as a red tubular structure of approximately 0.2-0.3 cm diameter and variable length ranging from 0.3 to 1.8 cm, which presented positive spectral deflections with Doppler. The ADA examination provides a typical biphasic behavior with a small systolic component and greater diastolic velocity.

Apical longitudinal strain was defined as the average of 4 apical segments corresponding to the ADA from the three apical views at rest and during stress, considering any increase of strain percentage as normal.

Coronary flow reserve velocity with dipyridamole stress echocardiography

Basal systolic and diastolic coronary flow velocity measurements of the anterior descending artery were performed, although only peak diastolic values were considered for the analysis of CFR in this study. After baseline measurements, dipyridamole was administered according to protocol without changing the transducer position and the Doppler sample, with ongoing monitoring and recording of the velocities obtained during the infusion period and within one minute following termination.

CFR was calculated dividing maximum peak flow in hyperemic conditions by resting values. Normal values were ≥ 2 .

Two echocardiography specialists with experience in this method performed the offline measurements of all the parameters described, considering the mean values of three consecutive periods.

Regional wall motion abnormalities

A left ventricular model divided into 17 segments was used. Each segment was assigned a score varying from 1 (normal) to 4 (dyskinetic), to generate a wall motion score index (WMSI) at rest and at maximum stress. Positivity was associated with abnormal wall motion in at least two contiguous segments (WMSI max > WMSI at rest).

Follow-up and definition of events

Mean follow-up was 36 ± 9.3 months. It was conducted by phone, by trained professionals who were unaware of the dipyridamole stress echocardiography outcomes. All the patients were followed up.

Major events were defined as death, myocardial infarction, myocardial revascularization by any method, and hospitalization due to cardiac reason.

Statistical analysis

Quantitative variables were expressed as mean \pm standard deviation or median and interquartile range, depending on whether distribution was parametric or not. The t-test or Wilcoxon test was used to compare two groups, depending on whether the distribution was parametric or not, respectively. Qualitative variables were expressed as percentages, and statistical significance was determined with the chi-square test. A two-tailed p value < 0.05 was considered statistically significant. The area under the ROC curve and the sensitivity and specificity were determined. The linear correlation between two quantitative variables was measured using Pearson's correlation coefficient. Analyses were performed with Stata statistical software (Version 10.0, Stata-Corp, Texas, USA).

RESULTS

Apical longitudinal strain measurements were successful in 142 patients (94.6%); 8 patients were excluded due to inadequate windows. Mean age was 68.3 ± 9.6 years, and 50.7% were men.

Patients were divided into 2 groups, based on the apical longitudinal strain results: Group 1, patients with normal apical longitudinal strain behavior at rest/under stress, and Group 2, patients with abnormal longitudinal strain behavior at rest/under stress (Figure 1). A total of 87 patients (61.3%) were included in Group 1 and 55 (38.7%) in Group 2. As for their baseline characteristics, patients in Group 2 were older, with no other differences between the populations (Table 1).

Behavior of apical longitudinal strain under pharmacological stressor

There were no differences in apical longitudinal strain at rest between groups (Group 1 $-21.3 \pm 6.7\%$, vs Group 2 $-21.1 \pm 6.3\%$, p = NS), but significant differences were observed at peak dipyridamole effect (Group 1 $-26.1 \pm 7.3\%$ vs Group 2 $-17.8 \pm 5.8\%$, p < 0.0001) (Table 2).

Analysis of wall motion and CFR under pharmacological stress

Preserved contractility on dipyridamole was found in 87 patients in Group 1 compared to 37 patients in Group 2 (97.7% vs. 67.3%, p < 0.01) (Table 2).

Patients with normal apical longitudinal strain response (Group 1) showed a lower index of visually assessed WMSI (Group 1 1.04 ± 0.13 vs Group 2 1.21 ± 0.31 , p < 0.001) and a higher ADA FR (Group 1 2.6 ± 0.5 vs Group 2 1.6 ± 0.3 ; p < 0.001).

CFR and apical longitudinal strain changes in dipyridamole effect at rest and at peak showed a positive correlation (Pearson's r coefficient = 0.89, p < 0.0001).

Long-term follow-up

Twenty-four major events were reported during long-term follow-up: 3 deaths, 3 non-fatal myocardial infarctions, 10 revascularizations and 8 hospital admissions for cardiac causes. Group 1 had 8 events (9.2%) and 16 Group 2 16 (29.1%), p <0.01. Group 2 had

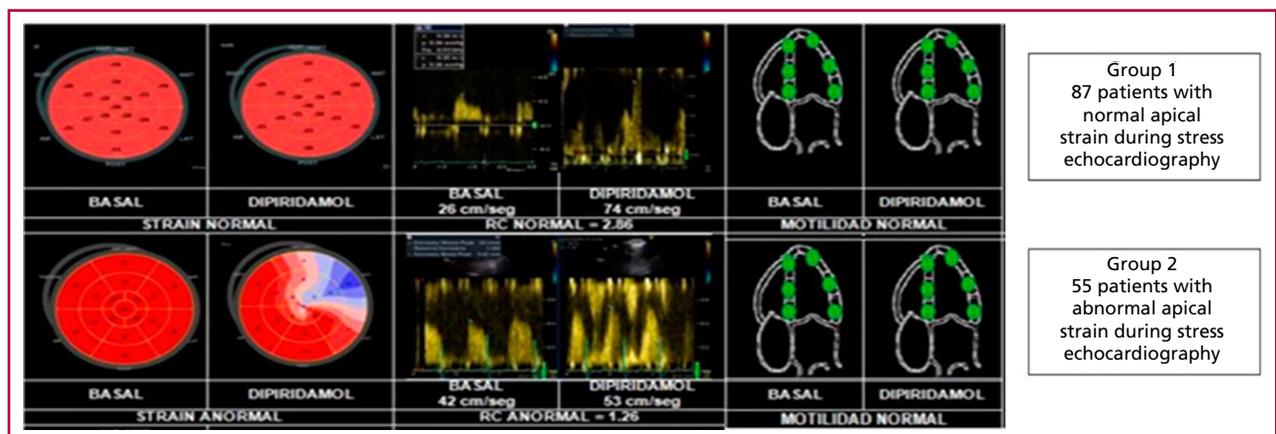


Fig. 1. Basal and post-stress apical strain

more events than Group 1: mortality 5.55% vs 0% (p = 0.02), acute myocardial infarction 5.55% vs 0% (p = 0.02) and need for revascularization 11.1% vs 4.5% (p = NS) (Table 3).

At the end of follow-up, Group 1 showed improved event-free survival (Group 1 = 90.8% vs Group 2 = 70.9%, log rank p < 0.01, HR: 3.69; CI 95%: 1.5-8.6) (Figure 2).

In multivariate logistic regression analysis adjusted by age, apical longitudinal strain was an independent predictor of events (OR 1.07, 95% CI 1.02-1.09, p = 0.002), better than regional analysis of wall motion (OR 0.955, 95% CI 0.90-1.01, p = 0.1).

DISCUSSION

The present study demonstrates that apical longitudinal strain behavior during dipyridamole stress echocardiography is similar to that of the ADA CFR, and is also an independent predictor of events in patients with known or suspected coronary artery disease.

We detected 24 major events during follow-up. Patients with normal apical longitudinal strain had a significantly lower event rate than those without increased strain. CFR correlated perfectly with strain results, even in the absence of visual contractility disorders (Figure 1).

Over the past 34 years, dipyridamole stress echocardiography has proven to be an excellent resource for the diagnosis and prognosis of patients with coro-

nary artery disease. However, limitations include subjectivity in the analysis of wall motion and contractile response blockade in patients under treatment with beta-blockers. (5, 9)

Adding CFR measurement, an excellent parameter to comprehensively assess the vascular tree, improved the diagnostic sensitivity of dipyridamole stress echocardiography. Consequently, even in the absence of visual contractility disorders but with low CFR, a higher rate of coronary events was observed during follow-up. (3,10,11) However, since CFR measurement requires a certain level of training, it is not available in all echocardiography laboratories.

The so-called third generation of the dipyridamole stress echocardiography protocol consisted of the addition of wall motion quantification through the assessment of longitudinal myocardial deformation using the two-dimensional speckle tracking echocardiography. This new tool improved numerical calculation of the drug effect on regional and global ventricular mechanics, providing an easy and fast interpretation of the test result through the polar map. (12)

Speckle tracking is becoming increasingly available in echocardiography laboratories, and dipyridamole is the ideal stressor for its implementation, considering the lower heart rate and the minimal displacement of thoracic movements compared to exercise and dobutamine echocardiography. Longitudinal strain assesses the most vulnerable subendocardial

Variable	Group 1 Normal apical strain 87 patients (61.26%)	Group 2 Reduced apical strain 55 patients (38.74%)	P value
Male subjects, n (%)	42 (48.6%)	29 (53%)	ns
Age, years (mean ± SD)	66,6 ± 10.27	70,2 ± 9.31	0.02
High blood pressure n (%)	64 (73.4%)	46 (83.3%)	ns
Dyslipidemia, n (%)	62 (70.8%)	38 (68.5%)	ns
Diabetes, n (%)	22 (25.5%)	26 (37.9%)	ns
Smoking, n (%)	65 (75%)	41 (74.3%)	ns
Previous coronary heart disease, n (%)	19 (21.8%)	21 (37.9%)	ns

SD: standard deviation

Table 1. Baseline characteristics of the population

Variable	Group 1 n=87	Group 2 n=55	P
Apical strain at rest	-21.3 ± 6.7	-21.1 ± 6.3	ns
Apical strain under stressor	-26.1 ± 7.3	-17.8 ± 5.8	< 0.01
Preserved contractility under stressor	85 (97.7%)	37 (67.3%)	< 0.01

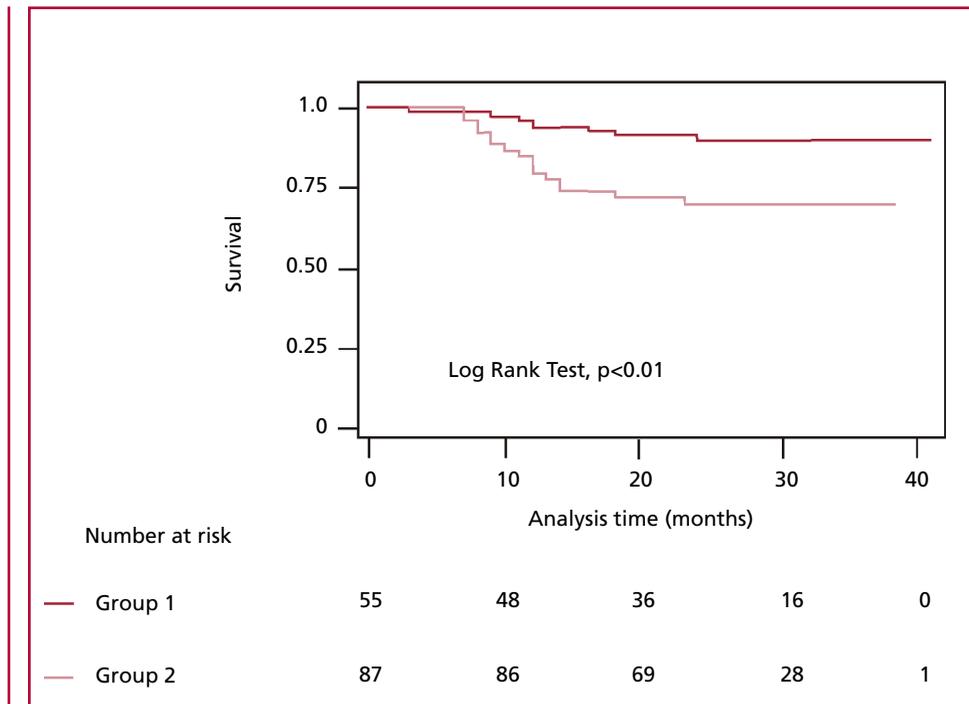
Table 2. Dipyridamole Stress Echocardiography Outcomes

Variable	Group 1 n=87	Group 2 n=55	P
Combined, n (%)	8 (9.2%)	16(29.1%)	0.002
Mortality, n (%)	0 (0%)	3 (5.55%)	0.02
AMI, n (%)	0 (0%)	3 (5.55%)	0.02
Need for revascularization, n (%)	4 (4.5%)	6 (11.1%)	ns
Hospitalizations, n (%)	4 (4.5%)	4 (7.27%)	ns

AMI: Acute myocardial infarction

Table 3. Major events

Fig. 2. Survival curve of the groups. Kaplan Meier



fibers to ischemia, thus presenting higher sensitivity for detecting incipient contractility disorders. Although ejection fraction is the most used left ventricular global function parameter, several studies have shown that in ischemic conditions, there is an early impairment of regional longitudinal function even in the presence of normal ejection fraction. (13)

A previous study performed by our group demonstrated that the analysis of 2D strain significantly improved the echocardiography sensitivity to detect coronary artery disease regarding the analysis of contractility (83.3% vs. 50%; $p = 0.001$), without involving its specificity (100%). (7) Identical conclusions are drawn from other groups' research, which also proved the added value of two-dimensional strain measurement to traditional visual wall motion analysis. In a study by Cusma-Piccione et al, (14) 52 patients underwent dipyridamole stress echocardiography using a protocol at low and high doses, demonstrating that global longitudinal strain (GLS) was superior compared to changes in wall motion index in single-vessel disease (sensitivity 84% vs 44%, specificity 92% vs 55%, positive predictive value 96% vs 73%, negative predictive value 68% vs 26%, respectively, $p < 0.001$). Nucifora et al showed that a GLS of -17.4% (sensitivity 83% and specificity 77%) provides a significant incremental value over the Duke Clinical Score for the identification of patients with obstructive coronary artery disease on multislice computed tomography. (15)

An excellent correlation between the behavior of the apical regional longitudinal strain and the ADA CFR was also demonstrated in that study. Myocardial contractility requires adequate perfusion. A 30-35% decrease in blood flow results in wall motion impair-

ment with a drop in regional and eventually global left ventricular systolic function. (16-18) It has been reported that the increase in flow and CFR elicited by the vasodilator stressor is expressed as an increase in systolic deformation by 2D strain, (7) possibly due to improved microcirculation conditions in myocardial fibers (Gregg effect). The Gregg effect postulates that the increase in perfusion pressure enhances the microvascular volume and opening of ionic channels; the greater intracellular calcium availability is responsible for better conditions of myocardial fibers, translating into ventricular mechanical efficiency. (19) Conversely, coronary flow steal as ischemic response is manifested as 2D strain impairment. In this regard, Clemmensen et al assessed exercise capacity, GLS and CFR in 57 heart-transplanted patients. A very good correlation was observed between GLS on exertion and CFR ($r = 0.8$; $p < 0.0001$). Patients with improved CFR increased GLS by $5.4 \pm 2\%$ in absolute values on exertion, whereas those with reduced CFR increased GLS by only $0.8 \pm 2.8\%$, showing a strong dependence of longitudinal deformation on CFR. (20) High feasibility of simultaneous measurement of apical longitudinal strain and CFR was demonstrated. (7)

In view of the information analyzed, the behavior of apical regional strain and CFR of the ADA are highly correlated, and both parameters provide equivalent diagnostic information. Consequently, if both determinations cannot be made, performing one of them could be enough and representative of both.

A study assessing the behavior of global and regional longitudinal strain in dobutamine stress echocardiography showed that regional strain measurement in the ADA territory increased sensitivity for detecting

coronary artery disease in that vessel. This was not the case in segments irrigated by the circumflex and the right coronary artery, in which visual wall motion analysis was superior. This lower performance of longitudinal strain to assess the posterior circulation is probably secondary to reduced lateral resolution as depth of field increases, and at high frequencies the speckles of medial and especially basal segments are more difficult to follow; in addition, detecting involvement in the ADA territory is associated with worse prognosis compared to other segments. (21)

A recent study by Simone et al on dipyridamole magnetic resonance imaging demonstrated that longitudinal strain analysis by future-tracking has incremental prognostic value for detecting events during follow-up, similar to that observed in our study. (22)

Another important study on a population of 3410 patients demonstrated the independent effect of the ADA CFR on contractility in predicting adverse events. (6)

Further advantages of longitudinal strain analysis include a short learning curve—making it an easy-to-use tool even for less experienced operators—, less interobserver variability compared to other parameters such as ejection fraction or visual wall motion analysis, and the fact that only a few minutes are required for the analysis, so it does not take significantly longer to complete the test. Conversely, strain limitations include little capacity of a baseline value to predict stress test outcomes, as was demonstrated in a previous study published by our group. (23,24)

Finally, it is worth noting that it is difficult to find a gold standard for the comparison of the different tools used; therefore, follow-up to assess major adverse events is the best way to know which of the parameters used had the greatest prognostic implication. Quantitative analysis of CFR and strain were significantly better than detecting visual disorders, highlighting that there were significant differences in mortality, revascularization, and hard events—such as death and myocardial infarction— between groups.

Limitations

This was a retrospective study on a small population with a short follow-up time.

A significant group of patients did not undergo coronary angiography, particularly those without visual wall motion abnormalities.

The present study was restricted to the ADA territory, due to the high feasibility of measuring its coronary reserve.

Finally, a small group of patients were assessed under anti-ischemic drugs, which may reduce contractile abnormalities during stress.

CLINICAL IMPLICATIONS OF THE STUDY

Quantitative objective parameters beyond visual contractility disorders need to be assessed in daily stress echocardiography practice if patient prognosis is to be

defined more accurately. CFR values in the ADA territory and/or regional longitudinal strain are necessary tools for patient management after stress echocardiography.

CONCLUSIONS

In a significant proportion of patients, there is no correlation between apical longitudinal strain and visually assessed wall motion analysis. Apical longitudinal strain correlates best with physiological standards such as coronary flow velocity reserve for defining long-term prognosis. Abnormal apical longitudinal strain during dipyridamole stress echocardiography predicted poor outcomes, irrespective of wall motion.

Quantitative stress echocardiography is possible, feasible and useful during dipyridamole stress echocardiography.

Conflicts of interest

Dr. Jorge Lowenstein is speaker to General Electric. The rest of the authors have no conflicts of interest..

(See authors' conflict of interests forms on the web/Additional material.)

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