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The Behavior of Regional Longitudinal Strain Depends on Coronary Flow Reserve in a Simultaneous Analysis during Dipyridamole Stress Echocardiography

El comportamiento del strain longitudinal regional depende de la reserva coronaria en un análisis simultáneo durante el eco estrés con dipiridamol.

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ABSTRACT

Background: The relationship between regional and global longitudinal strain and coronary flow reserve has been poorly studied.

Objectives: The primary aim of this study was to compare the behavior of apical and global longitudinal strain with the coronary anterior descending artery flow reserve and the secondary aim was to compare these responses with the visual analysis of wall motion during dipyridamole stress echocardiography.

Methods: A retrospective study was performed including 179 patients (50.3% men, n=90) with mean age 68.7 ± 7.8 years. Coronary flow reserve was measured at peak dipyridamole effect, simultaneously with longitudinal strain and the visual analysis of contractility. Patients were divided into two groups: Group 1: Coronary flow reserve ≥ 2 and Group 2: < 2 . Apical strain was defined as the average of 4 apical segments and global strain as the average of the 17 segments. Any increase in strain was considered normal.

Results: One hundred and thirteen patients (63.12%) were included in Group 1 and 66 (36.87%) in Group 2. Apical strain: 96.77% of Group 1 patients increased their strain values with stress, while in Group 2, 95.31% worsened their strain values ($p < 0.0001$). Global Strain: 82.8% of Group 1 patients increased their values, while in Group 2, 78.8% worsened their values ($p < 0.01$). Post dipyridamole wall motion analysis: 96.46% of Group 1 patients had preserved wall motion and only 54.5% of Group 2 showed this behavior (only 4 patients evidenced increased apical strain).

Conclusions: There was a close correlation between coronary flow reserve and apical longitudinal strain which was superior to the use of global longitudinal strain. Apical strain showed a better correlation with anterior descending artery coronary flow reserve than with the visual analysis of contractility.

Key words: Echocardiography, Stress/methods - Echocardiography, Doppler - Myocardial Contraction/physiology - Dipyridamole - Fractional Flow Reserve, Myocardial - Coronary Vessel/Diagnostic Imaging

RESUMEN

Introducción: Está poco estudiado el comportamiento del strain longitudinal regional y global en relación al valor de la reserva coronaria.

Objetivos: Comparar el comportamiento del strain longitudinal apical y global con el valor de la Reserva coronaria de la arteria descendente anterior y secundariamente comparar estas respuestas con el análisis visual de la motilidad parietal durante el eco estrés con dipiridamol.

Materiales y métodos: Estudio retrospectivo de 179 pacientes (edad 68.7 ± 7.8), 90 hombres (50.3%). En el pico del efecto de dipiridamol se midió la reserva coronaria, simultáneamente al strain longitudinal y el análisis visual de la contractilidad.

Fueron divididos 2 grupos: Grupo 1: Reserva coronaria ≥ 2 y Grupo 2: < 2 . El strain apical se definió como el promedio de 4 segmentos apicales y global de los 17 segmentos. Se consideró normal a todo incremento del strain.

Resultados: 113 pacientes (63.12%) se incluyeron en el Grupo 1 y 66 (36.87%) en Grupo 2. Strain apical: el 96.77% del Grupo 1 incrementaron su valor con el apremio, mientras que en grupo 2 el 95.31% presentaron caída del mismo ($p < 0.0001$). Strain global: el 82.8% del Grupo 1 presentaron incremento de sus valores, en cambio en el Grupo 2 el 78.8% empeoró ($p < 0.01$). Análisis de la motilidad parietal post dipiridamol: el 96.46% del Grupo 1 tenían motilidad parietal conservada y el 54.5% del grupo 2 (sólo en 4 pacientes aumentó el strain apical).

Conclusiones: Se comprobó una estrecha correlación entre la reserva coronaria y el strain longitudinal. El strain longitudinal apical resultó ser superior al global. El strain apical demostró tener una mejor correlación con la reserva coronaria que con el análisis visual de la contractilidad.

Palabras clave: Ecocardiografía de Estrés/métodos - Ecocardiografía Doppler - Contracción Miocárdica/fisiología - Dipiridamol - Reserva del Flujo Fraccional Miocárdico - Vasos coronarios/diagnóstico por imagen

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INTRODUCTION

Dipyridamole stress echocardiography is one of the recommended pharmacological stress tests for the diagnosis and prognosis of coronary heart disease. Although it is attributed less sensitivity in single vessel lesions, its use in high doses during a short infusion period with the addition of atropine and/or hand-grip allows a diagnostic accuracy similar to dobutamine and with lower major adverse effects. (1, 2)

One of the main limitations of stress echocardiography is the subjective assessment of wall motion, which is influenced by the operator's experience, the quality of the ultrasound window and the technical equipment. Anterior descending artery (ADA) coronary flow reserve and speckle tracking myocardial strain analysis have been therefore incorporated in an attempt to increase the diagnostic yield. (3)

Coronary flow reserve (CFR) assessment in the distal portion of the ADA provides an additional prognostic value to wall motion analysis, increasing the study sensitivity of epicardial coronary lesions, with only a slight decrease of sensitivity, considering that its evaluation integrates information from the macrovascular coronary territory and microvascular function. (2-5)

On the other hand, a better knowledge of myocardial structure has allowed a more detailed understanding of the cardiac contraction mechanism. The analysis of longitudinal function, which evaluates the most vulnerable subendocardial fibers to ischemia by means of speckle tracking strain has been shown to increase the sensitivity of the study compared with the visual analysis of wall thickening. (6)

Compared with other stress techniques, dipyridamole stress echocardiography provides the ideal conditions for this type of analysis due to the lower increase of heart rate and the better window quality owing to the absence of hyperventilation.

The primary aim of this study was to compare the behavior of global longitudinal strain (GLS) and regional apical longitudinal strain (RApLS) with CFR in the ADA territory. The secondary objective was to compare these responses with the visual analysis of wall motion during dipyridamole stress echocardiography.

METHODS

Population

This was a retrospective, descriptive, comparative, single-center study, including 179 patients studied in our center with dipyridamole stress echocardiography during a 2-year period (January 2017 to January 2019). Mean age was 68.7 ± 7.8 years and 90 patients (50.3%) were men.

All patients had to have normal global and regional function at rest to be selected for the study. Only patients with previous myocardial infarction in a territory different from the ADA or history of myocardial revascularization without wall motion abnormalities at rest were included in the study.

Structural heart disease of different etiology (for example, valve disease), complete left bundle branch block, atrial

fibrillation, or inadequate ultrasound window, were considered exclusion criteria.

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

Stress echocardiography

Patients had to fast for at least 4 hours and should not consume xanthine infusions and/or medications 12 hours prior to the study. Stress consisted in the intravenous infusion of dipyridamole 0.21 mg/kg/min in 4 minutes. 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 (ASE) guidelines.

Ejection fraction (EF) was obtained automatically.

The ADA was visualized as a red tubular structure of approximately 0.2 to 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.

Global longitudinal strain was analyzed from 4, 3 and 2-chamber apical views and was considered as the average of 16 segments. Regional apical longitudinal strain was defined as the average of the 4 apical segments corresponding to the ADA from the three apical views at rest and during stress, considering any increase of percent strain as normal (Figure 1).

Delta GLS and delta RApLS were defined as the difference between baseline and stress global and apical strain values, respectively.

Coronary flow reserve velocity with dipyridamole stress echocardiography

Anterior descending artery systolic and diastolic coronary flow reserve velocity measurements were performed, although only peak diastolic values were considered for the analysis of CFR in this study. After baseline measurements, without changing the transducer position and the Doppler sample, dipyridamole was administered according to protocol, with permanent monitoring and recording of the velocities obtained during all the infusion period and one minute after its conclusion.

Coronary flow reserve was calculated dividing maximum peak flow in hyperemic conditions by resting values. Normal values were ≥ 2 (Figure 1).

Two echocardiography specialists with experience in this method performed the off-line measurements of all the parameters described, considering the average values of three consecutive periods.

Regional wall motion abnormalities

A left ventricular model divided into 16 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 ($\text{WMSI}_{\text{max}} > \text{WMSI}_{\text{at rest}}$) (Figure 1).

Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median and interquartile range, according to their parametric or non-parametric distribution. Student's t test or the Wilcoxon test were used to compare between groups, according to their parametric or non-parametric distribution, respectively. Qualitative variables were expressed as percentages and statistical significance was assessed with the chi-square test. A two-tailed p value <0.05 was considered statistically significant. Specificity and sensitivity and the area under the ROC curve (AUC) were determined. Pearson's correlation coefficient was used to assess the linear correlation between two quantitative variables. Stata 10.0 software package (StataCorp, Texas, USA) was used to perform the statistical analyses.

Ethical considerations

The study was evaluated and approved by the institutional Ethics Committee. An informed consent, authorized by a relative or person responsible was requested for each patient included in the study.

RESULTS

Patients were divided into two groups according to their CFR: 113 patients (63.13%) with CFR ≥2 were assigned to Group 1 and 66 patients (36.87%) with CFR <2 to Group 2.

Patients in Group 1 were younger than those in Group 2 (65.9±10.27 vs. 72.2±9.31 years, p<0.02). There were no other significant differences between both groups. Baseline population characteristics are described in Table 1.

No differences were observed in the resting values of GLS and RApLS between both groups; GLS: Group 1: -19.8±4.8 vs. Group 2: -20.27±2.6 p=NS; RApLS; Group 1: -25.41±4.75 vs. Group 2: -26.73±7.6 p=NS (Table 2).

Pharmacological stress results

Global longitudinal strain and RApLS increased during stress in Group 1 patients with a significant worsening in Group 2 patients (GLS: Group 1: -22.98±4.31 vs. Group 2: -17.82±2.70, p<0.0001; RApLS: Group 1: -28.43±5.6 vs. Group 2: -22.78±7.41, p<0.0001) (Table 2).

Global longitudinal strain increased in 82.8% of Group 1 patients and worsened in 78.8% of Group 2 patients (p<0.01) (Table 2). The negative predictive value (NPV) was 78.8% (95% CI 67.5-86.9%) and the positive predictive value (PPV) was 90.8% (95% CI 83.9-94.9%). Specificity (Sp) was 83.9% (95% CI=72.8-91.0%), sensitivity (S) was 87.6% (95% CI=80.3-92.5%) and the AUC was 0.84.

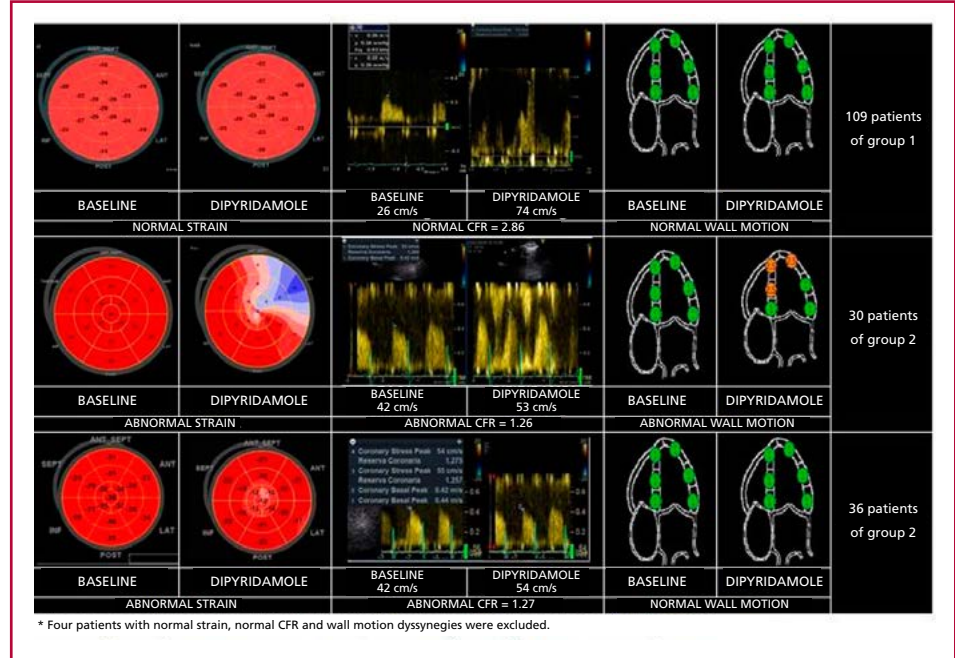
Regional apical longitudinal strain increased with stress in 96.77% of Group 1 patients and decreased in 95.31% of Group 2 patients (p<0.0001) (Table 2); NPV: 95.6% (95% CI 87.8-98.5%), PPV=96.8% (95% CI 89.0-99.1%); Sp: 97% (95% 89.9-99.2%); S: 95.2% (95% CI 86.9-98.4%) and AUC: 0.92.

The analysis of the relationship between GLS and RApLS rest-stress delta and CFR evidenced that the lower the GLS and RApLS delta, the lower the CFR, and that this correlation was slightly higher for RApLS (correlation coefficient between GLS and CFR: 0.54 (p<0.001), and between RApLS and CFR: 0.59 (p<0.001) (Figures 2 and 3).

Wall motion analysis

The analysis of posterior wall motion response to dipyridamole showed that 109 Group 1 patients (96.46%) had preserved wall motion after pharmacological stress. From the total number of Group 2 patients, 36 (54.5%) presented preserved wall motion and among them, RApLS was increased in only 4 patients (11.1%).

Fig. 1. Examples of resting and peak coronary flow reserve and global and apical longitudinal strain and their relationship with wall motion abnormalities.



Variable	Group 1 CFR ≥ 2 113 patients (63.12%)	Group 2 CFR < 2 66 patients (36.88%)	p value
Male gender, n (%)	55(48.67%)	35(53.03%)	NS
Age (years \pm SD)	65.9 \pm 10.27	72.2 \pm 9.31	< 0.02
Hypertension, n (%)	83 (73.45%)	55 (83.3%)	NS
Dyslipidemia, n (%)	80 (70.8%)	45 (68.2%)	NS
Diabetes, n (%)	29 (25.66%)	25 (37.8%)	NS
Smoking, n (%)	85 (75.22%)	49 (74.24%)	NS
Previous AMI, n (%)	25 (22.12%)	25 (37.8%)	NS
CABG, n (%)	10 (8.8%)	9 (13.6%)	NS
Three-vessel disease, n (%)	8 (7.07%)	7 (10.36%)	NS

AMI: Acute myocardial infarction. CABG: Coronary artery bypass grafting

Table 1. Baseline population characteristics

Variable	Group 1 CFR ≥ 2	Group 2 CFR < 2	p value
Resting global strain (%)	-19.8 \pm 4.8	-20.27 \pm 2.6	NS
Peak global strain (%)	-22.98 \pm 4.31	-17.82 \pm 2.7	< 0.0001
Resting apical strain (%)	-25.41 \pm 4.75	-26.73 \pm 7.6	NS
Peak apical strain (%)	-28.43 \pm 5.6	-22.78 \pm 7.41	<0.0001
Delta apical strain	3.94	-3.37	<0.0001
Delta global strain	2.85	-1.5	<0.0001
Baseline ejection fraction (%)	58.41 \pm 10.09	57.50 \pm 8.96	NS
Peak ejection fraction (%)	65.44 \pm 9.44	62.23 \pm 9.12	NS

Table 2. Results

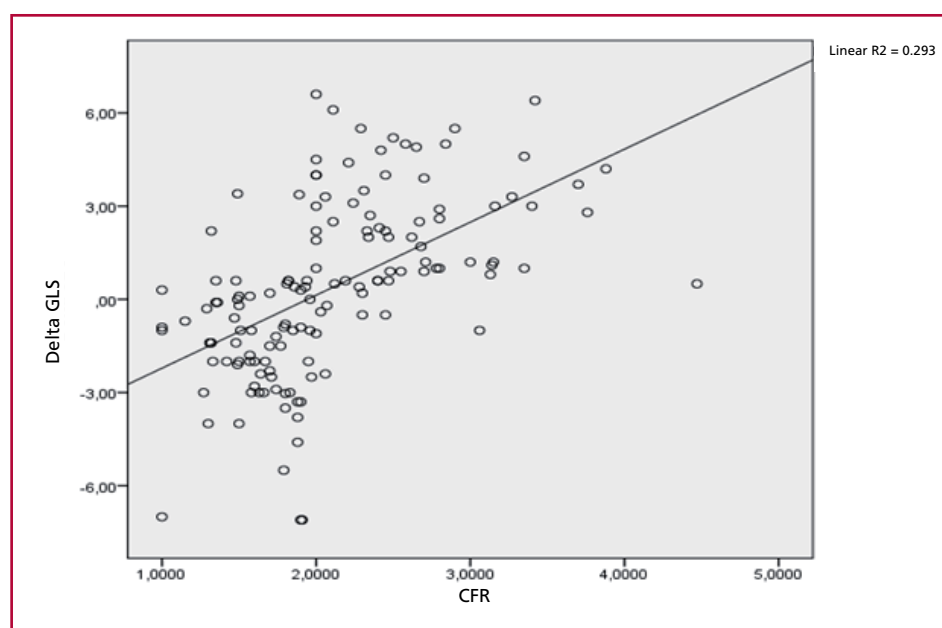


Fig. 2. Relationship between delta global longitudinal strain and coronary flow reserve. Pearson's R correlation coefficient: 0.54 ($p < 0.001$). GLS: Global longitudinal strain. CFR: Coronary flow reserve.

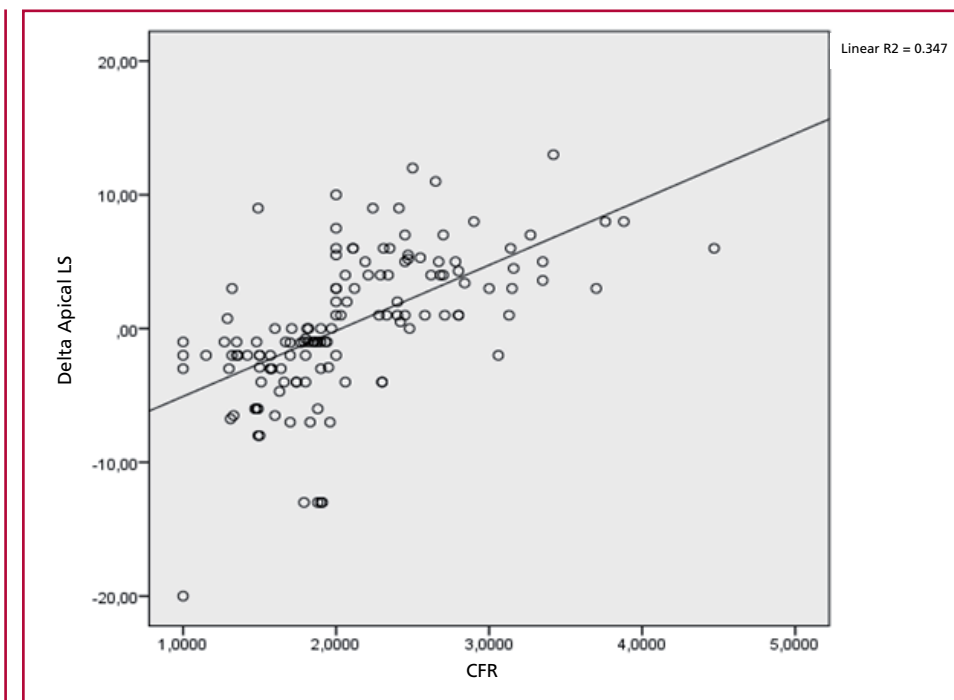
Systolic ventricular function analysis

Baseline ventricular EF of the total population was $57.96\% \pm 9.94\%$ and during stress it was $63.84\% \pm 9.29\%$. No statistically significant differences were found in the analysis of EF among Group 1 and Group 2 patients, either in baseline or stress conditions (Group 1(baseline): $58.41\% \pm 10.9\%$ and

Group 1 (stress): $65.44\% \pm 9.44\%$; Group 2 (baseline): $57.50\% \pm 8.96\%$ and Group 2 (stress): $62.23\% \pm 9.12\%$; $p = \text{NS}$).

When only patients with regional dyssynergy were compared, no significant statistical differences were found in EF between Group 1 and 2 patients, either in baseline or stress conditions (Group 1(baseline):

Fig. 3. Relationship between delta regional apical longitudinal strain and coronary flow reserve. Pearson's R correlation coefficient: 0.54 ($p < 0.001$). Apical LS: Apical longitudinal strain. CFR: Coronary flow reserve.



56.69% \pm 6.1% and Group 1 (stress): 63.02% \pm 7.35%; Group 2 (baseline): 55.65% \pm 7.32% and Group 2 (stress): 2.75% \pm 5.59%; p =NS).

The analysis of Group 2 patients (CFR <2) without regional dyssynergy showed the same EF behavior (baseline: 59.7% \pm 5.81% and stress: 62.61 \pm 5.63; p =NS).

DISCUSSION

During a period of 30 years we have used dipyridamole stress echocardiography to establish the diagnosis and prognosis of coronary heart disease patients. Use of high doses over a brief period of time (4 minutes) allowed increasing the diagnostic yield and successfully stratify the prognosis of these patients. However, the limitation of a subjective analysis and blockade of the contractile response in patients under betablocking treatment were the main drawbacks for its use. (5, 7)

The incorporation of CFR to the measurement improved diagnostic sensitivity even in an important group of patients without visual contractility disorders but with low CFR who evolved with high rate of coronary events during follow-up. (8)

For this reason, same as angiography constitutes the method of reference for the anatomical assessment of epicardial coronary arteries, CFR has become the diagnostic gold standard to evaluate the maximal vasodilator capacity to different stimuli, constituting an excellent parameter to assess the integrity and microfunctionality of the whole coronary bed, including the microcirculation. (3, 9)

The third generation of the Dipyridamole Stress Echocardiography protocol consisted in the addition of quantification by myocardial longitudinal deforma-

tion using the 2D speckle tracking strain technique. This new tool improved the numerical calculation of the drug effect on global and regional ventricular mechanics. (10)

Longitudinal strain evaluates the most susceptible myocardial fibers to ischemia, thus presenting greater sensitivity to detect incipient contractility disorders. Although ejection fraction is the most used left ventricular global function parameter, several studies (11) have shown that in ischemic conditions, there is an early impairment of regional longitudinal function in the presence of normal ejection fraction (which is unable to detect regional disorders).

To evaluate this phenomenon, we refer to a study performed by our group showing that both contractility as well as CFR assessed by dipyridamole stress echocardiography evidenced excellent specificity (100%); sensitivity, however, was not ideal. When 2D strain analysis was incorporated, a significant increase in the test sensitivity was observed compared with the contractility analysis (83.3% vs. 50%; p =0.001, respectively), without affecting its specificity (100%). (6)

This study again confirmed the absence of a relationship between the predictive value of GLS at rest and CFR in patients with coronary heart disease, as shown in a previous study published by our group (12) analyzing 123 patients undergoing different ischemia evocative tests. The results showed that that 2D GLS at rest did not predict the stress echocardiography result or the presence of significant coronary heart disease. Another study confirmed that LS does not have memory of transient ischemic insults produced by stress echocardiography. (13)

Myocardial contractility requires adequate perfu-

sion. A coronary flow decrease of 30-35% impairs wall motion with a fall of regional systolic function and eventually left ventricular global function. (14-16)

An increase in flow and CFR elicited by vasodilator stress is expressed as an increase of systolic deformation produced by 2D strain, (6) probably because it improves the microcirculatory conditions in the myocardial fibers (Gregg effect). Conversely, coronary flow steal as ischemic response is manifested as 2D strain impairment.

The Gregg effect postulates that the increase in perfusion pressure enhances the microvascular volume and opening of ionic channels; the greater intracellular Ca^{2+} availability is responsible for better conditions of myocardial fibers, translating into ventricular mechanical efficiency. (17)

The feasibility of measuring CFR simultaneously with 2D strain was evaluated in a previous study including 41 patients and excluding 3, one due to deficient pulsed Doppler signal of the ADA, limiting CFR analysis, and two owing to suboptimal window for 2D strain. The final feasibility of the study was 93% (95% CI 81-98.1). (6)

The study of Cusma-Piccione et al. (18) on the additive value of GLS with respect to wall motion, included 52 patients with dipyridamole stress echocardiography at low and high doses, and demonstrated that GLS was superior compared with changes in the wall motion index in single vessel disease (S 84% vs. 44%, Sp 92% vs. 55%, PPV 96% vs. 73% and NPV 68% vs. 26%, respectively, $p < 0.001$).

In the literature, several works correlated strain and coronary heart disease. The study of Nucifora et al. showed that a GLS of -17.4% (S: 83%, Sp: 77%) provides a significant incremental value on Duke's clinical score to identify patients with obstructive coronary disease in multislice computed tomography. (19). It should be pointed out that the analysis of regional strain was the parameter with best diagnostic accuracy and angiographic correlation for ischemic events, as reported by Shimoni et al. (20)

Another stimulating work was reported by Clemmensen et al. evaluating exercise capacity, GLS and CFR in 57 patients with heart transplantation. A good correlation was observed between stress GLS and CFR in the ADA territory ($r=0.8$; $p<0.0001$). Patients with better CFR increased the absolute GLS values by $5.4 \pm 2\%$ during stress, whereas those with reduced CFR only increased it by $0.8 \pm 2.8\%$, evidencing a strong dependency of longitudinal strain with CFR. The latter group also had a significant reduction of their physical capacity. (21)

A publication on CFR and contractile reserve reported by Cortigiani et al. with 375 diabetic patients undergoing dipyridamole stress echocardiography, negative for ischemia, analysed the integration of the triple functional evaluation (wall motion index, CFR and contractile reserve assessed by ventricular elastance), and concluded that decreased CFR does

not always correlate with wall motion abnormalities. (22) This finding postulates two theories; on the one hand ongoing antiischemic therapy decreases diagnostic sensitivity, and on the other hand, impaired CFR may reflect the presence of angiographically mild to moderate coronary heart disease or microvascular disease, which do not alter wall motion during stress.

Previous studies, shared by our personal experience, have shown that patients with low CFR, even in the absence of wall motion abnormalities have worse prognosis. (23) The behavior of strain is an additional information that correlates with CFR, but the information of strain per se has diagnostic and prognostic power, so if both CFR and strain cannot be performed, the performance of one of them may be sufficient and representative.

The main result of our study was to clearly demonstrate that the behavior of ADA GLS depends on the CFR of that territory. When both values are normal dyssynergies in the corresponding territory are exceptional. However, an important group of patients with reduced CFR and strain showed no visual wall motion abnormalities.

Moreover, the correlation between lower delta strain values (baseline vs. stress) and the presence of lower CFR values has been well established, with a significant correlation coefficient.

Limitations

This was a retrospective study, with a short follow-up period and low number of patients, so we do not have as yet prognostic data about the results of the two populations. However, in previous studies we observed that in patients with low CFR, even in the absence of visual dyssynergies, the prognosis was not favorable, with a high annual rate of events. (23)

An important group of patients did not undergo coronary angiographic studies, especially those with no visual wall motion abnormalities.

The present study was limited to the ADA territory due to the high feasibility of assessing CFR.

Finally, a small group of patients was evaluated under ant-ischemic medication, which could have decreased contractile anomalies during stress.

Clinical implications

When all the proposed and assessed parameters in this work are normal, we are undoubtedly encountering a negative diagnosis for ischemia and a good prognosis for the patient, different from an abnormal response of the three parameters evaluated.

Of note is the group of patients with decreased coronary flow reserve and strain, in whom the prognosis will be different regardless of whether they have microvascular disease or epicardial artery lesion.

In daily practice, subtle or ambiguous contractile abnormalities in the ADA territory with abnormal CFR and reduced RAPLS should be considered positive in the final report.

CONCLUSIONS

Global and regional apical longitudinal strain depends on the value of coronary flow reserve in the anterior descending artery territory.

The visual analysis of wall motion was unable to identify almost half of patients with decreased coronary flow reserve and strain.

This last group of patients should be closely monitored owing to the high probability of events.

Conflicts of interest

All the authors of this work have contributed to the study and accepted the Editorial Committee conditions, confirming no direct or indirect conflicts of interest.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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