

Performance of Myocardial Work as a Marker of Ischemia in Dipyridamole Stress Echocardiography

Comportamiento del trabajo miocárdico como marcador de isquemia en el ecocardiograma estrés con dipiridamol

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ABSTRACT

Background: There is scarce evidence about the assessment of myocardial work during dipyridamole stress echocardiography (DSE). **Objective:** The aim of the present study was to evaluate the performance of myocardial work during DSE and to define its differences between patients with and without myocardial ischemia.

Methods: This retrospective study included 30 patients; mean age was 69.9 ± 10 years and 45% were men.

Results: Eight patients (27%) presented ischemia. After dipyridamole infusion, global myocardial work index (GWI) and global constructive work (GCW) decreased in the groups with and without ischemia. In patients with ischemia, global wasted work (GWW) increased and global work efficiency (GWE) decreased. In patients without ischemia, GWW decreased while GWE remained unchanged or significantly improved.

Conclusions: In DSE myocardial ischemia was associated with increased GWW and decreased GWE. These findings warrant further studies to elucidate the responsible mechanisms.

Key words: Myocardial work - Dipyridamole stress echocardiography - Strain

RESUMEN

Introducción: Existe escasa evidencia sobre la evaluación del trabajo miocárdico (TM) durante el eco estrés con dipiridamol (EED).

Objetivos: Estudiar el comportamiento del trabajo miocárdico durante el EED y definir sus diferencias entre pacientes con y sin isquemia.

Material y métodos: Estudio retrospectivo. Se incluyeron 30 pacientes, 45 % hombres, con una edad de $69,9 \pm 10$ años.

Resultados: Ocho pacientes (27%) presentaron isquemia. Con el apremio con dipiridamol, en los grupos con y sin isquemia disminuyó el índice de trabajo miocárdico global (ITG) y el trabajo constructivo global (TCG). En los pacientes con isquemia se evidenció un aumento del trabajo desechado global (TDG) y una disminución de la eficiencia del trabajo miocárdico (ETG), mientras que en los pacientes sin isquemia el TDG disminuyó y la ETG se mantuvo o mejoró significativamente.

Conclusiones: La isquemia en el EED se acompañó de un mayor desaprovechamiento y una menor eficiencia del trabajo miocárdico. Dichos hallazgos justifican más estudios al respecto, para desentrañar los mecanismos responsables.

Palabras clave: Trabajo miocárdico - Ecocardiograma estrés dipiridamol - Strain

INTRODUCTION

Dipyridamole stress echocardiography (DSE) is a first-line stress test for the diagnosis and/or prognosis of coronary artery disease, particularly in patients unable to exercise maximally. Although the sensitivity of DSE is lower in single-vessel disease, the diagnostic accuracy is similar to that of dobutamine stress echocardiography in protocols that include atropine or

handgrip exercise in the final stage and employ a fast infusion rate. (1)

This type of stress also allows for the measurement of other parameters with a high degree of feasibility. These parameters include coronary flow reserve (CFR) in the left anterior descending (LAD) coronary artery and the assessment of myocardial deformation using speckle-tracking echocardiography. This is pos-

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sible because the drug has vasodilator properties and produces lower increase in contractility and in heart rate (HR) compared to dobutamine, which makes it an ideal complement for the analysis of myocardial strain. It has been previously demonstrated that the information provided by these techniques increases the sensitivity of the test without significantly affecting its specificity and provides additional prognostic value. (2)

While myocardial strain quantification offers a more sensitive means of detecting early signs of myocardial dysfunction that may otherwise go undetected in subjective wall motion analysis, one of its limitations is its dependence on myocardial loading conditions. It has been suggested that measuring the pressure-strain loop is an effective method for estimating myocardial work (MW). This allows for a more comprehensive evaluation of myocardial function by considering the global myocardial work index (GWI), the global constructive work (GCW), the global wasted work (GWW), and the global work efficiency (GWE). The GWI is derived from the area of the pressure-strain loop. The GCW represents shortening of the myocardium during isovolumetric contraction and lengthening of the myocardium during isovolumetric relaxation. The GWW represents the amount of work that is not useful in this context (lengthening of the myocardium during systole or shortening during isovolumetric relaxation). Finally, the GWE is defined as the ratio between constructive work and the sum of constructive and wasted work. (3)

The aim of the present study was to evaluate the behavior of different MW parameters during an DSE study in a consecutive population of patients and the differences between those with and without ischemia.

METHODS

Study population

This single-center study had a retrospective and analytical design. The study population consisted of consecutive patients who underwent DSE in the echocardiography laboratory of Hospital de Clínicas José de San Martín between August 2023 and March 2024. Patients with atrial fibrillation, inadequate ultrasound window and significant (moderate or severe) valvular heart disease or congenital heart disease were excluded from the study.

Stress echocardiograph

Patients fasted for at least 4 hours and avoided xanthine containing beverages or medications 12 hours before the study. Dipyridamole was the stressor used in intravenous infusion of 0.84 mg/kg/min over 4 minutes. (4) A Vivid E95 ultrasound machine (GE HealthCare) with a 5 MHz matrix array transducer was used to acquire two-dimensional images at a frame rate of 60 to 70 frames/second. The evaluation of the standard ultrasound parameters was performed following the guidelines of the American Society of Echocardiography (ASE). (5)

Analysis of longitudinal strain and myocardial work

Global longitudinal strain (GLS) was analyzed semiautomatically from the apical 4-, 3-, and 2-chamber views and was con-

sidered as the average of the values obtained in a 17-segment model. The first step to calculate myocardial work was to visualize the opening and closure of mitral and aortic valves from the apical 3-chamber view and to measure cuff blood pressure in the patient's right arm to obtain the pressure-strain loop. The analysis of the pressure-strain loop allowed us to determine the following parameters: GWI, GCW, GWW and GWE according to the myocardial deformation during the different periods of the cardiac cycle (Figure 1). These values were measured both at baseline and 8 minutes after the end of dipyridamole infusion, and the delta was defined as the difference between both measurements. (6)

Ethical considerations

The study was approved by the local ethics committee.

Statistical analysis

All calculations were performed using IBM SPSS Statistics 20 software package. Qualitative variables were expressed as percentages and quantitative variables as mean and standard deviation or median and interquartile range according to their distribution. The groups were compared using the corresponding hypothesis tests (chi square test, Student's t test or the Mann-Whitney test) depending on the type of variable and distribution of data. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 30 patients were consecutively included; mean age was 69.9 ± 10 years and 45% were men. One third had a history of coronary artery disease and the prevalence of cardiovascular risk factors was high. The main reason for performing DSE was to assess the preoperative risk of cardiac events before peripheral vascular intervention. These characteristics are summarized in Table 1.

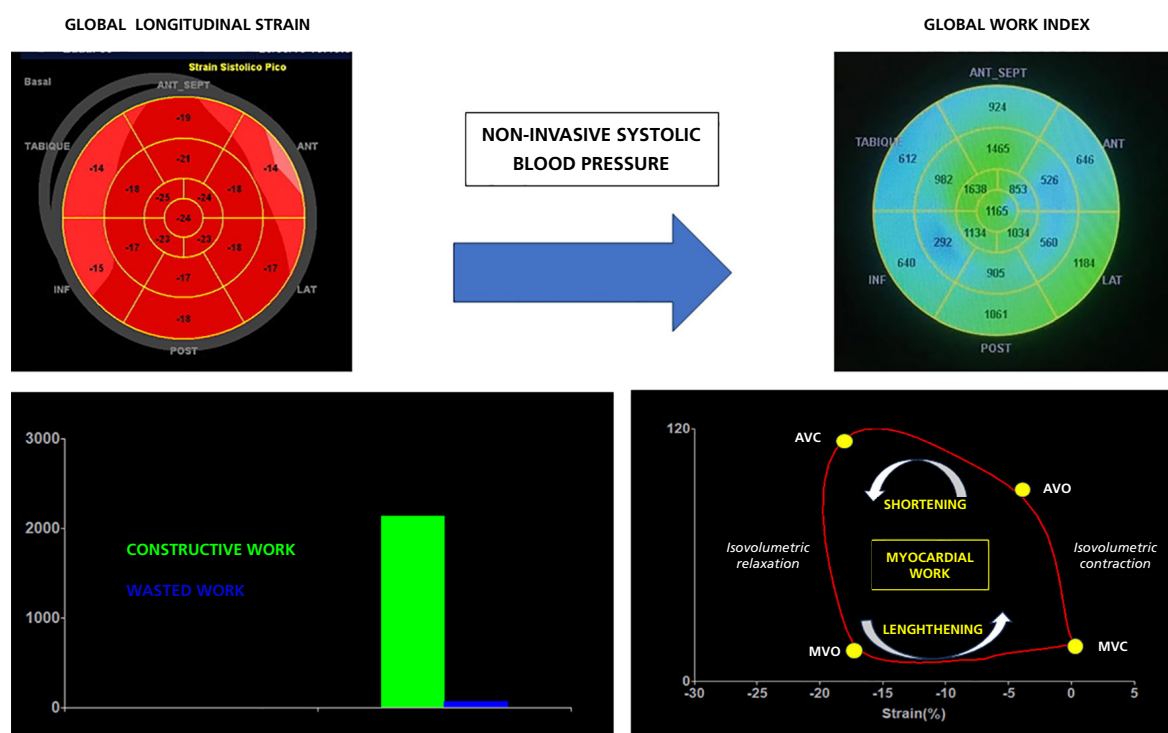
Myocardial ischemia was evident in 8 patients (27%) according to the visual analysis of wall motion. These patients exhibited a trend toward higher prevalence of previous MI and cardiovascular risk factors. There were no differences in the baseline HR and blood pressure at rest and during pharmacologic stress. Left ventricular volumes had no differences in patients with and without ischemia but left ventricular ejection fraction (LVEF) and GLS were significantly lower in patients with dipyridamole-induced ischemia. The CFR in the LAD coronary artery was lower in patients with ischemia, and these patients had a trend toward lower contractile reserve. Table 2 summarizes the characteristics of the 2 groups.

When the different parameters of MW were analyzed, GWI and GCW decreased in both groups, although there was a tendency for a smaller decrease in patients without ischemia. In contrast, the GWW and GWE performed differently. In patients with ischemia, the GWW increased and the GWE decreased. In patients without ischemia, the GWW decreased while the GWE remained unchanged or significantly improved (Table 2, Figure 2 and 3)..

DISCUSSION

Stress echocardiography is still a first-line test for the diagnosis and prognosis of coronary artery disease.

Fig. 1. Based on the values of global longitudinal strain (top-left) and noninvasive arterial pressure, the global myocardial work index (GWI) is automatically determined (top-right). The opening and closing times of the mitral and aortic valves are used to assess myocardial deformation at different stages of the cardiac cycle (bottom).



AVC: aortic valve closure; AVO: aortic valve opening; LVP: left ventricular pressure; MVC: mitral valve closure; MVO: mitral valve opening.

Table 1. Patients' clinical characteristics

Variable	Value
Age (years)	69.9 ± 10
Male sex	45%
HTN	78%
DM	33%
Smoking habits	16%
Obesity	26%
Previous MI	29%
PCI	8%
Beta blockers	44%
ACEI	32%
ARB	32%
Statins	56%
Aspirin	43%

ACEI: angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; DM: diabetes mellitus; HTN: hypertension; MI: myocardial infarction; PCI: percutaneous coronary intervention.

About 20-30% of patients cannot exercise maximally and the use of high-dose dipyridamole administered over 4 minutes is an excellent option in this scenario.

However, the main limitation of this approach is the subjectivity inherent in visual analysis of wall motion, particularly in less experienced operators. This is a relevant consideration given that the drug does not increase contractility and heart rate in a proportionate manner to that observed with dobutamine, and that a considerable proportion of patients are already receiving beta-blocker therapy.

To address these limitations, the concurrent measurement of CFR in the LAD coronary artery and the analysis of myocardial deformation through two-dimensional strain have been proposed. The CFR allows for a comprehensive evaluation of the coronary vascular tree and numerous studies have demonstrated its significant prognostic value beyond the presence or absence of wall motion abnormalities. Therefore, its measurement is strongly recommended in all patients undergoing stress echocardiography. (8,9) Nevertheless, its implementation in routine clinical practice is limited due technical considerations, namely the necessity for an optimal configuration of imaging parameters, the fact that not all operators know how to use it, and economic reasons in our setting.

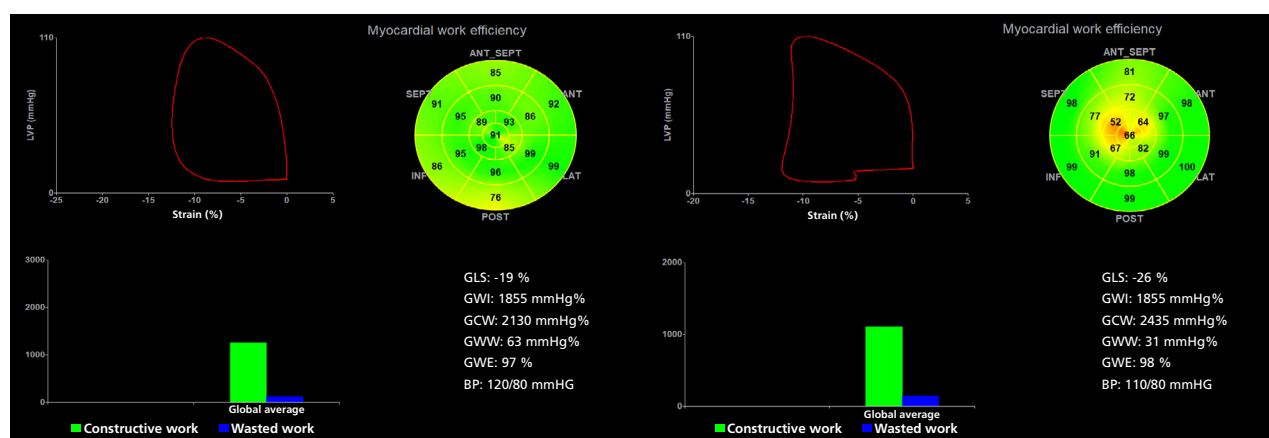
The quantification of myocardial deformation by analyzing GLS represents another valuable tool for enhancing the sensitivity of the test without signifi-

Variable	Ischemia (n=8)	No ischemia (n=22)	p
CLINICAL CHARACTERISTICS			
Male sex	50%	38%	0.601
Age (years)	73.6 ± 9.1	68.7 ± 10.1	0.293
HTN	100%	78%	0.225
DM	48%	29%	0.412
Previous MI	88%	10%	0.113
Beta blockers	60%	48%	0.467
ACEI	38%	30%	0.822
ARB	32%	28%	0.783
Statins	65%	52%	0.676
Aspirin	65%	35%	0.432
SBP (mm Hg)	130 ± 9	134 ± 15	0.603
Stress SBP (mm Hg)	127 ± 39	125 ± 25	0.893
DBP (mm Hg)	72 ± 7.5	77 ± 8	0.226
Stress DBP (mm Hg)	72 ± 12	72 ± 10	0.868
HR	67 ± 18	68 ± 10	0.871
Stress HR	82 ± 12	87 ± 17	0.532
ECHOCARDIOGRAPHIC PARAMETERS			
EDV (mL)	94 ± 57	79 ± 31	0.468
Stress EDV (mL)	95 ± 57	85 ± 36	0.645
ESV (mL)	55 ± 54	37 ± 24	0.521
Stress ESV (mL)	57 ± 56	35 ± 24	0.452
LVEF (%)	50 ± 14	56 ± 11	0.248
Stress LVEF (%)	49 ± 15	61 ± 11	0.031
Longitudinal strain (%)	-15 ± 4	-18.2 ± 4	0.099
Stress longitudinal strain (%)	-14 ± 5	-20.8 ± 4.1	0.003
CFR in the LAD coronary artery	1.6 ± 0.24	2.3 ± 0.35	0.001
LV contractile reserve	17%	37%	0.349
Wall motion score index	1.41 ± 0.49	1.11 ± 0.23	0.191
Stress wall motion score index	1.64 ± 0.41	1.10 ± 0.22	0.019
MYOCARDIAL WORK PARAMETERS			
GWI (mmHg%)	1493 ± 513	1946 ± 481	0.828
Stress GWI (mmHg%)	1164 ± 470	1850 ± 24	0.005
Delta GWI (mmHg%)	-329 ± 163	-96 ± 255	0.050
GCW (mmHg%)	1697 ± 572	2229 ± 612	0.068
Stress GCW (mmHg%)	1358 ± 580	2136 ± 640	0.014
Delta GCW (mmHg%)	-338 ± 183	-93 ± 312	0.081
GWW (mmHg%)	130 ± 105	123 ± 87	0.885
Stress GWW (mmHg%)	143 ± 93	82 ± 53	0.171
Delta GWW (mmHg%)	14 ± 95	-41 ± 64	0.108
GWE (%)	90 ± 9	93 ± 5	0.435
Stress GWE (%)	85 ± 12	95 ± 3	0.123
Delta GWE (%)	-5 ± 6	2 ± 3	0.019

Tabla 2. Clinical and echocardiographic characteristics of patients according to the presence of myocardial ischemia.

Quantitative variables are presented as mean ± standard deviation and qualitative variables as percentages. ACEI: angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; DBP: diastolic blood pressure; DM: diabetes mellitus; EDV: end-diastolic volume; ESV: end-systolic volume; GCW: global constructive work; GWE: global work efficiency; GWI: global myocardial work index; GWW: global wasted work; HR: heart rate; HTN: hypertension; LAD: left anterior descending; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; SBP: systolic blood pressure.

Fig. 2. Study of a patient without myocardial ischemia showing a decrease in GWW (baseline 63 mmHg% and stress 31 mmHg%) and stable GWE (baseline 97 mmHg% and stress 98 mmHg%). Left: baseline study; right: stress test



BP: blood pressure; GCW: global constructive work; GLS: global longitudinal stress; GWE: global work efficiency; GWI: global myocardial work index; GWW: global wasted work; LVP: left ventricular pressure

Fig. 3. In a patient with myocardial ischemia, we observed a decrease in GWE (baseline 91 mmHg% and stress 88 mmHg%) and an increase in GWW (baseline 113 mmHg% and stress 145 mmHg%). Left: baseline study; right: stress test.



BP: blood pressure; GCW: global constructive work; GLS: global longitudinal stress; GWE: global work efficiency; GWI: global myocardial work index; GWW: global wasted work; LVP: left ventricular pressure

cantly reducing its specificity. In this case, the slight increase in HR and contractility, which was previously regarded as a limitation of the method, is, in fact, an advantage. DSE is considered the ideal scenario for the use of two-dimensional strain. The analysis of the performance of subendocardial fibers, which are more sensitive to ischemia, allows for the detection of incipient abnormalities and helps in the interpretation of myocardial wall motion, as demonstrated in a study by Lowenstein et al. in which the inclusion of GLS increased the sensitivity of the test from 50% with visual analysis to 83.3% ($p = 0.001$). (2) The close relationship between the performance of CFR and GLS was demonstrated in a publication by Arbutti et al., in which both parameters were evaluated with DSE in a population of 179 patients. Both values showed a significant correlation, that was higher when the re-

gional strain of the apical segments was considered. (10)

Myocardial work assessment has the advantage of incorporating loading conditions to conventional two-dimensional strain and the pressure-strain loop is proportional to myocardial oxygen uptake. (11) Its usefulness has been demonstrated in numerous clinical scenarios such as patients with arterial hypertension, valvular heart disease, coronary artery disease, heart failure and cancer, among others. (12,13) However, there is little evidence on its usefulness during stress echocardiography. Recently, Borrie et al. analyzed 60 patients who underwent exercise stress echocardiography. Of these patients, 30% exhibited evidence of ischemia, as indicated by wall motion abnormalities. With exercise, GWI increased and GWE remained unchanged in individuals without ischemia while in

those with ischemia GWI remained unchanged (i.e., did not increase) and GWE showed a significant decrease (from 93% to 87%). This study determined that the best cut-off point for identifying patients with myocardial ischemia was a 25% increase in GWI, with a sensitivity of 90% and a specificity of 85%. (14) These findings suggest that this tool could have additional value in patients with a good ultrasound window. The study by Edwards et al. reaches similar conclusions. (15) One of the main limitations to the use of MW during exercise stress echocardiography is the quality of the ultrasound window and the elevated HR during exercise that hinders accurate analysis of myocardial wall motion during the cardiac cycle.

In a study using pharmacological stress echocardiography, Leitman et al. analyzed MW with the use of dobutamine in 119 patients without ischemia. Dobutamine stress echocardiography resulted in a decrease in all MW parameters despite improvement in GLS. The authors suggest that the dose of up to 40 mcg/kg/min until 85% of maximum heart rate is reached may have deleterious effects on contractility. (16) More recently, Liu et al. reported a study performed with adenosine in 78 patients with microvascular angina and evaluated the performance of MW according to the presence or absence of CFR. The main finding was that patients with microvascular disease (abnormal CFR) had increased GWW and decreased GWE, in addition to a trend towards a smaller increase in GWI and GCW. (17) Similar findings are reported in an abstract published by Lofrumento et al. in 50 patients with suspected macrovascular disease, where it is evident that the analysis of GWE and GWW has an additive role beyond GLS when implemented in a DSE. (18)

The results obtained in our study are in line with those studies evaluating MW with exercise and adenosine in terms of increased wasted work and decreased efficient work in patients with ischemia, which is related to the percentage of post-systolic strain. It should be noted that, in contrast to the effects observed during exercise, the use of vasodilators such as dipyridamole is expected to result in stable and potentially decreased blood pressure values. Consequently, it can be expected that the GWI and GCW will not increase or even decrease slightly during exercise.

Study limitations

This study has several limitations. Firstly, it is a retrospective study, which makes it difficult to draw comparisons between groups. Secondly, the number of patients involved is small, which limits the ability to perform regional analysis of the different MW parameters. Finally, there is no definition of the anatomical correlation with coronary artery lesions.

CONCLUSION

The introduction of new quantitative analysis tools, such as MW, could assist in the interpretation of signs

of myocardial ischemia in DSE. Further verification of these observations is required in larger patient cohorts with the inclusion of additional stressors such as exercise and dobutamine.

Conflicts of interest

None declared.

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

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