ORIGINAL ARTICLE

Contractile and Chronotropic Reserve Assessment in stress Echocardiography Studies Negative for Myocardial Ischemia

Valoración de la reserva contráctil y cronotrópica en estudios de eco estrés negativos para isquemia miocárdica

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ABSTRACT

Background: While the primary objective of the stress echocardiography (stress echo) is to assess wall motion abnormalities, evaluation of other variables, such as contractile reserve (CR) via elastance, and chronotropic reserve (ChR), may add prognostic value to the study. However, these are unusually evaluated or reported in most stress echo studies in our field.
Objectives: To compare clinical and echocardiographic characteristics in patients undergoing an exercise stress echo with negative results for myocardial ischemia based on the presence or absence of CR and ChR.
Methods: Retrospective study in 73 patients, with exercise stress echo and no ischemia. Patients were divided into three groups, based on the presence or absence of CR and ChR. Group 1: presence of both; Group 2: presence of either of the two, and Group 3: absence of both. The CR was established as the systolic blood pressure and end-systolic volume ratio, both at rest and under stress (normal value: >2), and the ChR was defined as a more than 80% increase in baseline heart rate.
Results: The study enrolled 73 patients (64% male, aged 63±12 years). Group 1 included 23 patients (62% male, aged 59.8±12.5 years); Group 2 included 29 patients (65% male, aged 60.7±13 years), and Group 3 included 21 patients (65% male, aged 68.8±7.8 years). Patients with no reserve were older and showed a tendency to higher prevalence of traditional risk factors, a longer history of AMI and increased use of beta blockers. In the echocardiographic study this group had lower values of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) both at rest and under stress, a larger ventricular mass, and less minutes of exercise in the exercise stress test. A binary logistic regression was performed using variables associated with the absence of CR and ChR. Age (OR 1.12, 95% CI 1.02-1.22; p=0.01) and GLS at rest (OR 0.68, 95% CI 0.51-0.90; p=0.008) were independently associated with the absence of both reserves. On a ROC curve, a GLS of -18% was the best cutoff point (area under the curve 0.72).
Conclusion: Patients with a stress echo negative for myocardial ischemia and absence of CR and ChR have a higher risk profile. This could be associated with a higher risk of cardiovascular events during the follow-up.

Keywords: Stress Echocardiography – Left Ventricular Contractile Reserve – Cardiac Chronotropy

RESUMEN

Introducción: Si bien el principal objetivo del ecocardiograma estrés (EE) es analizar los cambios en la motilidad parietal, el análisis de otras variables como la reserva contráctil (RCon) por el método de elastancia y la reserva cronotrópica (RCro) permiten agregar valor pronóstico al estudio. No obstante, las mismas no suelen analizarse ni informarse en la mayoría de los estudios de EE en nuestro medio.
Objetivos: Comparar las características clínicas y ecocardiográficas de pacientes a quienes se les realizó un EE con ejercicio negativo para isquemia miocárdica de acuerdo con la presencia o no de RCon y RCro.
Material y métodos. Estudio retrospectivo realizado sobre 73 pacientes con EE con ejercicio, sin isquemia. De acuerdo con la presencia o ausencia de RCon y RCro se los dividió en tres grupos. Grupo 1: presencia de ambas reservas; grupo 2: presencia de solo una reserva y grupo 3: ausencia de ambas reservas. La RCon se determinó mediante el cociente entre la tensión arterial sistólica y el volumen de fin de sístole tanto en reposo como en estrés (Valor normal: > 2) y la RCro se definió como el aumento mayor al 80% de la frecuencia cardíaca basal.
Resultados: Se incluyeron 73 pacientes (64% varones, edad 63 ± 12 años). En el grupo 1 se incluyeron 23 pacientes (62% varones, 59,8 ± 12,5 años), en el grupo 2, 29 pacientes (65% varones, 60,7 ± 13 años) y en el grupo 3, 21 pacientes (65% varones, 68,8 ± 7,8 años). Los pacientes sin ninguna reserva fueron más añosos y presentaron una tendencia a mayor prevalencia de los factores de riesgo tradicionales, más antecedentes de IAM y mayor uso de betabloqueantes. Desde el punto de vista ecocardiográfico, este mismo grupo presentó menores valores de fracción de eyección ventricular izquierda (FEVI) y strain longitudinal global (SLG) tanto en reposo como en esfuerzo, mayor masa ventricular, y en la ergometría menor cantidad de minutos de ejercicio realizado. Se realizó una regresión logística binaria con aquellas variables asociadas a la ausencia de RCon y RCro. La edad (OR 1,12, IC95% 1,02 – 1,22; p= 0,01) y el valor de SLG en reposo (OR 0,68, IC95% 0,51-0,90; p= 0,008) fueron las variables asociadas en forma independiente

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a la ausencia de ambas reservas. En una curva ROC, un valor de SLG de -18% fue el mejor punto de corte (área bajo la curva 0,72).
Conclusiones: Los pacientes con EE negativo para isquemia miocárdica, y que además presentan ausencia de RCon y RCro tienen un perfil de riesgo más elevado. Esto podría estar asociado a mayor riesgo de eventos cardiovasculares durante el seguimiento.

Palabras clave: Ecocardiografía de Estrés - Disfunción Ventricular Izquierda - Reserva del Flujo Fraccional Miocárdico

INTRODUCTION

Since it emerged by the end of the 1970s, stress echocardiography (stress echo) has been steadily growing and has become one of the main cardiovascular diagnostic techniques. Stress echo combines two-dimensional and Doppler echocardiography with a stress. For many years, the primary objective of the test was to assess regional and temporal wall motion abnormalities as specific evidence of myocardial ischemia. (1)

It is widely acknowledged that a completely normal test has an excellent negative prognostic value for the occurrence of cardiovascular events. However, because of a better understanding of coronary artery disease pathophysiology in the last few years, this type of diagnosis might not be enough to describe the complexity and heterogeneity of patients with coronary artery disease. Therefore, new assessment protocols adding other variables have been developed, such as the presence of pulmonary congestion, contractile reserve (CR), chronotropic reserve (ChR), and coronary flow reserve, each of them adding a separate prognostic value. (2)

CR is defined as the capacity of the myocardium to increase pumping upon inotropic stimulation and has a well-established prognostic value in multiple clinical scenarios. While several parameters have been described for assessment, it is highly recommended to determine elastance, which combines systolic blood pressure (SBP) with left ventricular end-systolic volume (LVESV), as it is less dependent on loading conditions and is, therefore, a better surrogate for the myocardial contractile function. (3,4)

Chronotropic competence during stress is easy to determine in the test, and its absence has been related to worse prognosis in some studies using exercise, inotropic agents, and vasodilators. (5)

Despite potential usefulness of the information provided by these two parameters, these have not been evaluated or reported in most stress echo studies performed in our field. Therefore, the objective of this study is to compare clinical and echocardiographic characteristics in patients undergoing an exercise stress echo with negative results for myocardial ischemia based on the presence or absence of CR and ChR.

METHODS

Population

This was an observational, retrospective, descriptive, comparative, single-center study. The study enrolled 73 patients to be assessed in the echography lab at Hospital de Clínicas José de San Martín. They had an exercise stress echo in 2021 reported as negative for myocardial ischemia considering the wall motion assessment. The average age of the patients was 61±12 years, and 64% were male.

The exclusion criteria were the presence of atrial fibrillation, an inadequate ultrasound window preventing proper monitoring of endocardial borders in order to estimate left ventricular volumes, and the presence of significant (moderate or severe) valvular disease or congenital heart disease.

Stress echocardiography

The study was performed according to clinical practice guidelines recommended for stress echo to assess ischemic heart disease. There were 4 imaging stages: baseline, low load (50w), peak stress, and immediate post-stress. The views used were the following: apical 4-, 3-, and 2-chamber, parasternal short axis on papillary muscles, and parasternal long axis. Blood pressure was monitored at the end of each stage, and heart rate was continuously monitored. End-of-study criteria were muscle exhaustion, having reached the highest HR expected for the patient's age, presence of significant angina or dyspnea, relevant changes in the ST segment (ST segment depression ≥4 mm or ST segment elevation >1 mm), hypertension (systolic blood pressure [SBP], ≥240 mmHg and/or diastolic blood pressure [DBP], ≥120 mmHg), or severe arrhythmias. Wall motion score assessment used the 17-segment model, where 1=normal, 2=hypokinesia, 3=akinesia, and 4=dyskinesia. The stress echo was negative for myocardial ischemia when the wall motion score under stress did not exceed that at rest. (6)

CR was estimated through elastance, defined as the SBP/LVESV ratio. CR was positive when stress/rest elastance ratio was higher than 2. ChR was positive when HR under stress increased by ≥80% from baseline HR. (7)

Patients remained fasting for at least 4 hours. A supine bicycle was used. The exercise followed the Astrand protocol.

A Vivid E9 & E95 echocardiograph (GE Healthcare) was used, with a 5 Mhz Matrix transducer, with two-dimensional image acquisition at a rate of 60-70 frames/second. Common echocardiographic parameters were evaluated based on the guidelines of the American Society of Echocardiography (ASE). (8)

Statistical analysis

The analysis was performed with the IBM SPSS® Statistics v20 statistical package. Nominal variables were expressed as percentage relative to the total number of cases, and quantitative variables were expressed as mean and standard deviation, or median and interquartile range, as applicable. Normal distributions were analyzed using Kolmogorov-Smirnov or Shapiro-Wilk tests. The statistical comparison across groups used the corresponding hypothesis testing (Student's t-test, Mann-Whitney U test, chi-square test) according to the type of variable and data distribution. Inter- and intra-observer variability was analyzed using the intraclass correlation coefficient. The statistical significance was set at a 0.05 threshold.

Ethical considerations

The study was approved by the Hospital de Clínicas Bioethics Committee and was performed based on the applicable rules governing observational trials and the principles set forth in the Declaration of Helsinki.

RESULTS

The most important clinical and echocardiographic characteristics of the 73 patients enrolled in the study are summarized in Tables 1 and 2.

Out of 73 study patients, 23 (32%) had positive ChR and CR; 29 patients (39%) had only one of the two, and 21 patients had both negative reserves (29%). Patients with both reserves were younger, had a lower cardiovascular (CV) risk profile, a lower beta blocker therapy use, no history of coronary disease, and better systolic function. Table 3 summarizes the characteristics of the 3 groups.

A binary logistic regression was performed using the variables associated with the absence of CR and ChR. Age (OR 1.12, 95% CI 1.02-1.22; p=0.01) and GLS at rest (OR 0.68, 95% CI 0.51-0.90; p=0.008) were variables independently associated with the absence of both reserves.

The ROC curve was used to determine that the best longitudinal strain cutoff point at rest to predict absence of ChR and CR was -18% (area under the curve 0.72; 95% CI 0.57-0.87), with 79% sensitivity and 52% specificity.

DISCUSSION

At present, the stress echo has a predominant role as a diagnostic and prognostic technique, especially for ischemic heart disease, by means of the identification of wall motion contractile abnormalities at rest and, mostly, induced by stress. (6) However, the percentage of studies on stress echo negative for ischemia has increased in the last few years,(2) probably due to a change in the characteristics of the study population, a higher number of patients under full antiischemic therapy, and less study patients' clinical pretests, particularly those with preserved LVEF. All of this might reduce the study diagnostic sensitivity for inducible ischemia. (9) As a result, patient's risk assessment based only on the analysis of wall motion abnormalities could be considered incomplete from the present pathophysiological perspective. In these patients, evaluating other parameters while performing the stress echo might help to improve risk grading. (10)

Considering knowledge gained about the pathophysiology of ischemic heart disease, several aspects need to be observed. Epicardial artery involvement, adequately diagnosed by means of segmental motion abnormalities, as well as factors such as microvascular, myocardial, and autonomic dysfunction, which are associated with a higher number of CV events and deaths, should be considered. The mechanisms may be found isolated or combined, and mutually enhanced. Therefore, assessing different pathophysi-

Table 1. Patients' clinical characteristics (n=73)

Variables	Value
Age (years)	61±12
Male	64%
HTN	66%
Diabetes	16%
Smoking	16%
Obesity	30%
Previous AMI	16%
Angioplasty	14.5%
MRSCABG	4.1%
Beta blockers	53%
Calcium channel blockers	6.5%
ACEI	32%
ARA II	32%
Statins	59%
Aspirin	43%

ACEI: angiotensin-converting enzyme inhibitors
AMI: acute myocardial infarction
ARA II: angiotensin II receptor antagonists
CABG: Coronary artery bypass grafting
HTN: hypertension

Table 2. Patients' echocardiographic characteristics (n=73)

BASELINE ECHOCARDIOGRAPHY	
Variable	Value
SBP (mmHg)	127±15
DBP (mmHg)	76±9
HR	70±11
Regional wall motion abnormality	15%
Wall motion score	1.09±0.26
End-diastolic volume (mL)	92±39
End-systolic volume (mL)	39±26
Ejection fraction (%)	58±8
Global longitudinal strain (%)	-19.1±3.7
STRESS ECHOCARDIOGRAPHY	
Minutes of exercise	9±3
SBP (mmHg)	175±22
DBP (mmHg)	89±10
HR	124±20
End-diastolic volume (mL)	83±41
End-systolic volume (mL)	66±27
LVEF (%)	66±10
Global longitudinal strain (%)	-21.1±4.6
Positive contractile reserve	52%
Positive chronotropic reserve	45%

DBP: diastolic blood pressure
HR: heart rate
LVEF: left ventricular ejection fraction
SBP: systolic blood pressure

Table 3. Characteristics of the different groups based on the presence of ChR and CR

Variable	Two positive reserves (n=23)	One positive reserve (n=29)	No positive reserves (n=21)	P
Male	62%	65%	65%	0.98
Age (years)	59.8±12.5	60.7±13	68.8±7,8	0.029
HTN	61%	65%	76%	0.17
Diabetes	6%	15%	25%	0.08
Smoking	25%	11%	15%	0.30
Obesity	31%	27%	35%	0.70
Previous AMI	0%	24%	24%	0.11
Beta blocker	30%	52%	71%	0.06
BASELINE ECHOCARDIOGRAPHY				
SBP (mmHg)	124±15	128±16	134±15	0.09
DBP (mmHg)	75±9	76±10	75±9	0.86
HR	67±11	71±11	73±12	0.14
LVEDV (mL)	89±29	87±41	104±50	0.33
LVESV (mL)	33±12	37±25	53±39	0.06
LVEF (%)	62±3	59±2	52±1,5	0.005
Longitudinal strain (%)	-20.6±2.3	-20.5±2.2	-16.8±4	0.001
STRESS ECHOCARDIOGRAPHY				
SBP (mmHg)	172±25	167±31	168±24	0.83
DBP (mmHg)	87±9	88±9	86±9	0.74
HR	129±17	121±24	119±19	0.01
Minutes of exercise	10±2,.9	9.2±2.4	7.4±3.2	0.02
LVEDV (mL)	72±30	76±33	104±56	0.02
LVESV (mL)	21±8,8	27±7,5	49±8	0.003
LVEF (%)	71±3	66±3	57±2,3	0.0001
Longitudinal strain (%)	-23.7±2	-22.5±2.1	-18.1±2	0.0001

AMI: acute myocardial infarction
DBP: diastolic blood pressure
HR: heart rate
HTN: hypertension
LVEDV: left ventricular end-diastolic volume
LVESV: left ventricular end-systolic volume
LVEF: left ventricular ejection fraction
SBP: systolic blood pressure

ological stages may offer a more global perspective to improve diagnosis and risk grading, and thus provide relevant information for the patient's follow-up and treatment, either with drugs or revascularization techniques. (11)

In this context, CR and ChR assessment becomes more relevant, as it may reveal further mechanisms with more individualized treatments and allow for screening of higher-risk patients. (2,5)

The Stress Echo 2020 study (2) developed and spread a new standard of practice in stress echo imaging: the ABCDE protocol for functional tests in and beyond coronary artery disease which consisted of 5 variables. The first step (A) is the classical study of segmental wall motion abnormalities and estimation of the wall motion score. The next step (B) is the study of B-lines by means of lung ultrasound, considered to be positive upon occurrence of two or more B-lines under stress. Step C is the CR assessment using the elastance method, which means estimating the

systolic blood pressure and end-systolic volume ratio both under stress and at rest. Step D is the study of the coronary flow velocity reserve assessed via pulsed-wave Doppler on the distal segment of the left anterior descending artery (LAD), measured as the relationship between the diastolic flow speed under stress and at baseline, with a normal value higher than 2. The last step (E) is to measure the ChR using the relationship between the maximum heart rate at peak stress and baseline, with a normal value higher than 1.80 for exercise and dobutamine and higher than 1.22 when using vasodilators, such as dipyridamole. This paper has shown that the higher the number of impaired study variables, the worse are patients' prognosis and mortality. Steps B, D, and E showed higher prognostic value. All and each one of the steps in the ABCDE protocol provide independent and incremental prognostic information, and can identify various patient's phenotypes and weaknesses that may potentially describe different therapeutic goals: myocardial ischemia in step A, pulmonary congestion with B-lines in step B, left ventricular contractile reserve in step C, coronary microvascular dysfunction in step D, and autonomic dysfunction in step E.

This segmented and complementary approach can be used for a pathophysiological identification of therapeutic goals to be applied in each situation. Patients with step A impairment might benefit from anti-ischemic treatment (beta blockers, calcium channel blockers, nitrite, and/or revascularization). Those with step B involvement might benefit from diuretics for pulmonary congestion. A reduced CR (step C) relates to asymptomatic LV dysfunction and a higher risk of heart failure, LV enlargement and fibrosis, so that treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists could be indicated. Microvascular dysfunction identified in step D may lead to statin recommendations. Step E, with a reduced chronotropic reserve, would indicate a low sympathetic reserve; these patients could have greater electrical instability, risk of arrhythmias and sudden death, and probably beta blockers should be considered. (2)

Stress Echo 2030 is a currently ongoing multicenter and prospective study aimed at recruiting more than 10 000 patients from 2021 to 2025 to be followed-up for 5 years (until 2030) in more than 20 controlled-quality laboratories, evaluating the ABCDE protocol in different clinical scenarios: coronary artery disease, valve disease, congenital heart disease, cardiomyopathies, among others. (12)

The present study selected two variables additional to the study on wall motion: ChR and CR. Patients can have CR if they have proper tissue perfusion, adequate metabolic exchange in the myocardial fiber, and preserved microcirculation. As described, the CR can be evaluated in several ways. Traditionally, it was assessed using an increased LVEF under stress (5-10%), although this method has two major limitations: strong reliance on loading conditions and high intra- and interobserver variability. It can also be evaluated through an improved wall motion score >20%, or increased systolic ejection volume, >20% on average. (13) Previous studies have shown that elastance assessment is a more accurate method to evaluate CR than an isolated LVEF in a stress echo. (11, 13) Normally, the SBP increases and the ESV decreases under stress, so that their ratio is doubled during a stress echo. Please note that stress echo studies with vasodilators use other cut-off values (>1.1 is considered normal), as the SBP and LVESV behave differently. Under normal conditions, the ventricular end-diastolic volume mildly increases with low loading and then decreases upon maximum stress reaching levels similar to those at rest; therefore, the LVEF is increased mainly at the expense of LVESV reduction. In addition, establishing the LVESV is simpler than assessing the LVEF, as this requires addition of the end-diastolic volume measure, with the resulting increased possibility of error. (14)

In a previous study with diabetic patients using dobutamine stress echo negative for ischemia, we observed that a peak SBP/LVESV indexed on the basis of body surface lower than 28 mmHg/mL/m2 was associated with a greater need for revascularization and a higher rate of infarction and death. These patients also had a lower LVEF at rest compared to patients with a preserved index. (11) Another study performed with dipyridamole stress echo in diabetic patients with no evidence of myocardial ischemia according to wall motion assessment showed that patients with combined absence of CR and coronary reserve of the LAD artery had a risk of death, infarction, or revascularization nine times higher than those with both reserves preserved. (10) Another study with patients with a history of heart failure (HF) and no history of coronary artery disease with a dipyridamole stress echo with no ischemia showed that patients with a low coronary reserve, ChR, and CR, had seven times more events at follow-up (death, AMI, HF hospitalization and stroke). (5)

As regards the second variable, the ChR, previous reports show that the impossibility of reaching the expected HR is an independent predictor of future events (15). Chronotropic incompetence is also considered an autonomic dysfunction marker. (9) This may be a pathophysiological reflection of a reduced response to adrenergic stimulation in β1 receptors, which may result from increased baseline sympathetic activity (reflected in a higher HR at rest) or a reduced adrenergic response capacity, both associated with autonomic dysfunction. It has been reported that these responses are related to a worse prognosis. (16) A study by Cortigiani L et al. performed with dipyridamole stress echo showed that the group of patients with an increased ChR of less than 1.22

Variable	OR	(95% CI)	p
Age	1.120	1.025-1.224	0.013
Longitudinal strain at rest	0.68	0.51-0.90	0.008
LVEF at rest	0.006	0.000-15.56	0.45
Beta blockers	0.53	0.11-2.49	0.42

Table 4. Multivariate analysis associated with the absence of CR and ChR

had a higher risk profile (HTN, diabetes, history of AMI or revascularization) and a worse prognosis at follow-up (death and non-fatal infarctions), regardless of the presence of myocardial ischemia and beta blocking therapy. (9) This was also observed in patients with exercise stress echo, where chronotropic incompetence was assessed (as the inability to reach 85% of their maximum predicted HR during exercise). Patients with chronotropic incompetence at the stress echo had a higher risk of AMI and cardiovascular death, regardless of the baseline LVEF, clinical characteristics, and the presence or absence of wall motion abnormalities. (16)

Our study showed that patients with absence of both reserves (CR and ChR) were older, had a more adverse CV risk profile, a higher percentage of beta blocking therapies, and longer history of coronary artery disease. In the echocardiographic study , they had worse systolic function, higher end-systolic volumes, a shorter time of exercise, and lower global longitudinal strain, which might be associated with a higher rate of CV events in a prospective follow-up of these patients.

Another advantage of introducing these techniques in stress echo studies is that CR and ChR assessment does not mean a more complex or longer study. Estimated assessment times for these parameters are 1-3 minutes longer than a conventional study. And these times change inversely based on the operator's experience (from 5 minutes for operators with little experience to less than 2 minutes in more experienced ones). (9)

This study also showed that the absence of both reserves is independently associated with patient's age and more reduced GLS, as compared to patients with preservation of both reserves. Theoretically and hypothetically, we may assume that absence of both reserves might represent a stage prior to asymptomatic systolic dysfunction.

One limitation of our work is its retrospective nature and a limited number of patients. We believe this may be the starting point for a prospective follow-up where we expect to confirm the prognostic value of the evaluated variables, in terms of clinical events.

Finally, the CR and ChR assessment in stress echo negative for ischemia can increase diagnostic sensitivity; this is particularly useful in patients with a moderate or low pretest risk and in those where a segmental wall motion assessment shows no changes and provides additional and complementary information about the prognosis and future therapeutic decisions. Adding assessment and grading steps allows us to analyze risk from a non-binary (positive vs. negative) perspective and gain pathophysiological information that helps to improve treatment.

Conflicts of interest

None declared.

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

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