ORIGINAL ARTICLE

Contractile reserve by left ventricular ejection fraction alone, or considering elastance. ¿Which is the best predictor of events after a Stress Echo without ischemia?

Reserva contráctil por fracción de eyección sola, o con elastancia. ¿Cuál es el mejor predictor de eventos luego de un ecoestrés sin isquemia?

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ABSTRACT

Background: The behavior of left ventricular ejection fraction (LVEF) during exercise is used to measure contractile reserve (CR). CR measured by elastance could have greater prognostic value.
Objective: To establish whether the measurement of CR by elastance adds long-term prognostic value to CR measured by LVEF in patients with a Stress Echo without myocardial ischemia.
Material and methods: Retrospective study, carried out in 904 patients with an exercise Stress Echo without ischemia. CR was assessed by LVEF and by elastance. Patients were divided into 2 groups: Group 1: presence of CR by LVEF (in turn this group was divided into 2 subgroups: Group 1A, CR with elastance present, and Group 1B: absence of CR by elastance), and Group 2: patients with absence of CR by LVEF. The follow-up was 17,7 ± 5,4 months. Outcomes considered were death, acute myocardial infarction (AMI), stroke, and cardiovascular hospitalization.
Results: 536 patients were included in Group 1, 200 (37,3 %) in Group 1A and 336 (62,7%) in Group 1B. In Group 2, 368 patients were included. At follow-up, patients in Group 2 had more events, 30 (8.1%) vs. 22 (2.6 %) (HR 3.14, 95% CI 1.95-5.9, log rank test p<0.001). Within G1, patients in Group 1B presented more events: 18(5.3%) vs 4 (2%) (HR 2.46 CI 95% 1.06-7.3, log rank test p<0.05). In the regression model, CR assessed by LVEF and additionally by elastance was the only significant outcome predictor (HR 3.2, 95% CI 1.83-5.6, p<0.001).
Conclusions: In an exercise Stress Echo negative for ischemia, CR behavior evaluated by elastance allowed us to identify a subgroup with a worse long-term prognosis in patients with normal LVEF response.

Keywords: Echocardiography, Stress - Myocardial Contraction - Ventricular Function, Left / physiology

RESUMEN

Introducción: El comportamiento de la fracción de eyección del ventrículo izquierdo (FEVI) durante el ejercicio se utiliza para medir la reserva contráctil (RC). La RC medida por elastancia podría tener mayor valor pronóstico.
Objetivo: Establecer si la medición de la RC por elastancia añade valor pronóstico a largo plazo en relación al comportamiento aislado de la FEVI en pacientes con un eco estrés sin isquemia miocárdica.
Material y métodos: Estudio retrospectivo, realizado en 904 pacientes con Eco Estrés con ejercicio sin isquemia. Se valoró la RC por FEVI y por elastancia. Se dividieron en 2 grupos: Grupo 1: RC por FEVI presente (a su vez este grupo se dividió en 2 subgrupos: Grupo 1 A, RC con elastancia presente y Grupo 1B: ausencia de RC por elastancia), y Grupo 2: pacientes con ausencia de RC por FEVI. El seguimiento fue de 17,7 ± 5,4 meses. Se consideraron como eventos: muerte, infarto agudo de miocardio (IAM), accidente cerebrovascular (ACV) y/o internación de causa cardiovascular.
Resultados: Del total del Grupo 1 (536 pacientes), 200 (37,3%) se incluyeron en el Grupo 1A y 336 (62,7%) en el Grupo 1B. En el Grupo 2, se incluyeron 368 pacientes. En el seguimiento, los pacientes del Grupo 2 tuvieron más eventos, 30 (8,1%) vs. 22 (2,6 %) (HR 3,14, IC95% 1,95-5,9, log rank test p<0,001). Dentro del G1, los pacientes del Grupo 1B presentaron más eventos: 18 (5,3%) vs 4 eventos (2%) (HR 2,46 IC95% 1,06-7,3, log rank test p<0,05). En el modelo de regresión, la elastancia fue la única variable predictora de eventos (HR 3.2, IC95% 1,83-5,6, p<0,001).
Conclusiones: En el Eco Estrés ejercicio negativo para isquemia, el comportamiento de la RC evaluada por elastancia permitió identificar un subgrupo de peor pronóstico a largo plazo en pacientes con comportamiento normal de la FEVI.

Palabras clave: Ecocardiografía de Estrés - Contracción Miocárdica - Función Ventricular Izquierda/fisiología

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INTRODUCTION

The concept of Contractile Reserve (CR), defined as the ability of the myocardium to increase its pump function in response to an inotropic stimulus, is universally known as a prognostic key for multiple pathologies. For its assessment, one of the most used parameter is the behavior of the left ventricular ejection fraction (LVEF) during exercise.

Its measurement is widely used to diagnose diseases, determine their severity, establish prognosis and guide therapy. However, its usefulness in assessing systolic function is limited, not only due to difficulties inherent in the quality of the images or ventricular geometry, but,also because it depends on various factors in addition to contractility , such as pre and afterload, heart rate, and ventricular synchrony. These variables are substantially modified during exercise, which limits the capacity of the LVEF as a specific surrogate of the contractile function. On many occasions, LVEF can be increased during exercise, even though the contractility decreases, for example due to the development of significant mitral regurgitation with the consequent afterload decrease. Conversely, LVEF can decrease in the presence of preserved contractility, secondary to an exaggerated hypertensive response with increased afterload, or by increased heart rate with decreased ventricular filling, especially in small and stiff ventricles, or in the presence of dyssynchrony; a typical example is the appearance of left bundle branch block during exertion. The most important factor is the ventricular afterload. (1)

Among the reference publications in systolic function study, we can mention the group of Suga et al, who since 1969 (2) have studied ventricular contraction and left ventricular performance in canine hearts through instant measurement of the pressure/volume ratio throughout the cardiac cycle. Their findings demonstrated that the pressure/volume curve is independent of load conditions, although it varies with changes in contractility, (3) constituting one of the most representative parameters in the evaluation of ventricular systolic function. This index, called Ventricular Elastance (elastance), is defined as the ratio between systolic blood pressure and left ventricular end-systolic volume. It has the advantages of having greater sensitivity than other parameters, and being able to globally assess systolic function both at rest and with effort. (4-6) As observed by the group of Picano et al, their behavior with exercise can show 3 responses: normal ascending (exertion values that double the baseline, related to high systolic blood pressure values with decreased end-systolic volume), abnormal biphasic (initial slight increase followed by a return to baseline), and abnormal flat (both pressure and volume remain unchanged during stress) (7)

Considering the findings of these previous investigations, we can infer that the evaluation of CR by elastance during stress with exercise could have a higher prognostic value than the isolated measurement of the CR reserve by LVEF in patients with negative Stress Echo for ischemia (8, 9), and even in early stages of cardiomyopathies.

OBJECTIVE

The objective of this study was to establish whether the measurement of CR by elastance adds long-term prognostic value to isolated LVEF behavior in patients with Stress Echo without myocardial ischemia.

METHODS

Population

In a retrospective, descriptive, comparative, single-center study, we included 904 patients, studied in our center, with an exercise Stress Echo during a 2 years period (January 2018 to December 2019). The average age of the patients was 61.92 ± 12.59 years; 509 patients (56.3%) were men.

Patients had to be older than 18 years, with Stress Echo eco negative for ischemia; patients with history of known myocardial disease, structural heart disease of another etiology (for example, valvular patients), complete left bundle branch block, with atrial fibrillation or inadequate ultrasound window, were excluded.

All patients underwent exercise Stress Echo, with reported normal global and regional function at rest, and dyssynergy absence during stress. Previously, all signed the informed consent accepting the performance of the test and the use of the data for scientific purposes.

Echocardiogram Stress

The patients remained fasting for at least 4 hours. To carry out the study, a stretcher with a Schiller brand supine bicycle was used. The exercise was performed according to the Astrand protocol.

A Vivid E9 or 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. The evaluation of the usual ultrasound parameters was performed according to American Society of Echocardiography (ASE) guidelines

Contractile Reserve Estimation by Ejection Fraction and Ventricular Elastance

LVEF was defined as the percentage that represents the stroke volume, defined as the difference between left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) related to the EDV. LVEF= [(EDV - ESV) / EDV] x 100.

Left ventricular elastance was defined as the ratio between systolic blood pressure (SBP) and left ventricular end-systolic volume (SBP/ESV).

LVEF and estimation of ventricular volumes were obtained automatically with manual corrections when warranted by endocardial visual monitoring. The final values resulted from the average of at least 2 measurements.

At each stage of the study protocol, blood pressure was recorded using an Omron automatic sphygmomanometer.

Contractile reserve valuation

Contractile Reserve (CR) was assessed by LVEF and by elastance. CR assessed by LVEF was considered present when the absolute increase in LVEF during exercise was at least 5 points, and CR assessed by elastance was considered when the stress/rest elastance ratio was equal to or greater than 2.

The operator who performed all the studies is certified as highly experienced in reading ventricular volumes as required for entry into the 2020 project led by Eugenio Picano . (10)

Major Events – Final Points

Major cardiovascular outcomes were death, acute myocardial infarction (AMI), cerebrovascular accident (CVA) and/or need for hospitalization due to cardiovascular causes, in the average follow-up of 17.7 ± 5.44 months.

Statistical analysis

Quantitative variables were presented as mean and standard deviation or median and interquartile range depending on whether the distribution was parametric or not. For the comparison of two groups, the Student's t test or Wilcoxon's test was used depending on whether the distribution was parametric or not, respectively. Qualitative variables were expressed as percentages and statistical significance was determined using the chi square test. All comparisons were bilateral, considering statistically significant values of $p < 0.05$. The variables that in the univariate analysis showed a relationship with a value of $p < 0.1$ were entered into a multivariate analysis using logistic regression. Data processing was performed with the statistical package SPSS 10.0 (SPSS Inc. Chicago, USA).

Ethical Considerations

The study was evaluated and approved by an institutional Research Committee. Informed consent was required, authorized by a relative or guardian of each patient included in the study.

Ethical considerations

Given that it was an anonymous, self-referential and voluntary participation survey, the SAC ethics committee waived an informed consent.

RESULTS

The 904 patients included in the study were divided into 2 groups. Group 1 included those patients who presented CR assessed by LVEF. This group in turn was divided into 2 subgroups: Group 1A: CR assessed by elastance present, and Group 1B: CR assessed by elastance absent. Group 2 included those patients with no CR according to LVEF. Coincidentally, in this group all patients had no CR according to elastance.

Of the total, 536 patients (59.29%) were included in Group 1, 200 (37.32%) in Group 1A and 336 (62.68%) in Group 1B; 368 patients (40.71%) were included in Group 2.

Group 2 patients were significantly older (63.58 ± 11.2 years vs. 60.78 ± 13. 3 years in group 1, $p < 0.001$). There were no baseline clinical differences between the patients in Group 1A and 1B. (Table 1 and Table 2).

Stress Echo Results

All patients had no myocardial ischemia at the double product achieved, in motility analysis and longitudinal strain behavior by speckle tracking.

There were differences in ventricular volumes changes with exercise between the different groups. Group 2 patients had a higher increment of delta indexed EDV (stress-rest) to Group 1: 3.22 ± 11.1 mL vs -1.10 ± 11.1 mL in Group 1, $p<0$,001; and less decrease in delta indexed ESV: -0.86±5.6 mL vs -3.83± 3.75 mL, respectively; $p< 0.001$.

G1A patients had a greater decrease in indexed ESV than G1B: delta stress-rest indexed ESV: -5.12 ± 3.3 mL vs -2.54±3.68 mL, respectively; $p<0.001$, as can be seen in Table 2.

Table 1. General baseline and stress characteristics. Group 1 vs. Group 2.

Variables	Group 1 (CR by LVEF+)	Group 2 (CR by LVEF -)	p
Age (years)	60.78 ± 13 .3	63.58 ± 11.2	0 .001
BMI (kg/m^2)	28.92 ± 5 .2	28.73 ± 4.9	NS
HBP (%)	44.7	55.3	0.1
DM (%)	20.1	18.3	NS
SBP at rest (mmHg)	125.49 ± 21.8	128.20 ± 21.4	NS
LVEF rest %	59.59 ± 8.4	58.79 ± 10.5	NS
EDVi (ml/m^2)	43.28 ± 12.85	45.53 ± 15.36	NS
ESVi at rest (ml/m^2)	17.5 ± 9.73	19.62 ± 2.3	NS
Stress SBP (mmHg)	188.12 ± 31.4	185.49 ± 30.1	NS
LVEF stress %	66.85 ± 8.4	60.6 ± 64	0.001
Stress HR (bpm)	131 ± 20	128 ± 19	NS
EDVi stress (ml/m^2)	42.18 ± 10.9	48.5 ± 11.2	0.001
ESVi stress (ml/m^2)	13.98 ± 3.2	18.76 ± 12.02	0.001
LVEF Variation	7.26 ± 1.22	1.81 ± 1.28	0.001
Elastance	1.88 ± 0.53	1.51 ± 0.41	0.05
Delta EDVi stress/rest	-1.10 ± 11.1	3.22 ± 11.1	0.001
Delta ESVi stress/rest	-3.83 .± 3.75	-0.86 ± 3.6	0.001

CR: Contractile Reserve; BMI: body mass index; HBP: high blood pressure; DM: diabetes mellitus; SBP: systolic blood pressure; EDVi: indexed end-diastolic volume; ESVi: indexed end-systolic volume; HR: heart rate; LVEF: left ventricular ejection fraction; NS: not significant

Follow -up Outcomes

Mean follow-up was 17.7 ± 5.44 months. Patients without CR (Group 2), presented a greater number of major events compared to those in Group 1: 30 (8.15%) vs 22 (2.59%) (HR 3.14, 95% CI 1.95-5.9; log Rank test p < 0.008). (Figure 1).

Subgroup 1A patients had 4 major events (2%) vs. 18 (5.35%) in Subgroup 1B (HR 2.46, 95% CI 1.06-7.3; log Rank test p < 0.05). (Figure 2).

Finally, a Cox Regression model was carried out in which all the variables with significance p < 0.10 were included. CR assessed by LVEF and additionally by elastance was the only significant outcome predictor (HR 3.22, CI 95% 1. 83-5.6), p < 0 .001),

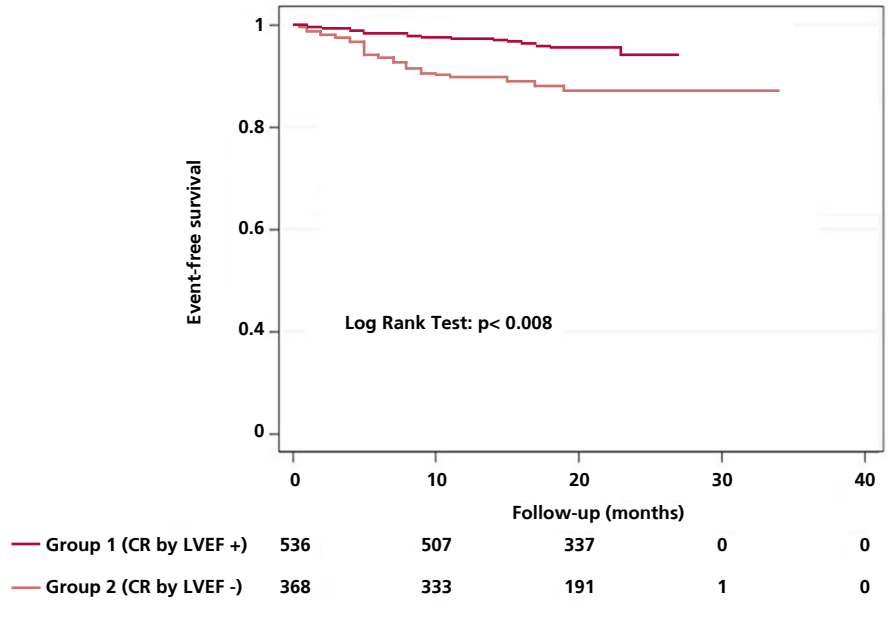
DISCUSSION

In the present study, two methods were compared to assess CR in a group of patients with exercise Stress Echo without inducible ischemia assessed by visual motility analysis and longitudinal strain by speckle tracking. CR was quantified in the usual way, and the ratio between systolic blood pressure and LV end-systolic volume, that is, ventricular elastance, at stress relative to rest, was measured.

Variables	Group 1A (CR by LVEF + and Elastance +)	Group 1B (CR by LVEF + and Elastance -)	p
Age (years)	59.41 ± 13.1	62.15 ± 13.5	NS
BMI	28.39 ± 4.9	29.45 ± 5.5	NS
HBP (%)	43.4	46.0	NS
DBT (%)	20.03	20.13	NS
SBP rest (mmHg)	126.79 ± 23.2	124.01 ± 20.51	0.1
LVEF rest %	60.23 ± 8.2	58.95 ± 8.6	NS
ESVi at rest(ml/m²)	16.4 ± 9.35	18.6 ± 10.11	NS
Stress SBP (mmHg)	194.22 ± 34.4	182.02 ± 28.4	0.001
Stress LVEF %	67.89 ± 8.6	65.81 ± 8.2	NS
Stress HR (bpm)	130±20	132 ± 20	NS
LVEF Variation	7.66 ± 1.1	6.86 ± 1.02	0.1
Elastance	2.21 ± 0.11	1.59 ± 0.11	0.001
Stress ESVi (ml/m²)	11.28 ± 6.2	16.06 ± 2.3	0.001
Delta ESVi stress/rest	-5.12 ± 3.3	-2.54 ± 6.5	0.001

CR: Contractile Reserve; BMI: body mass index; HBP: high blood pressure; DM: diabetes mellitus; SBP: systolic blood pressure; ESVi: indexed end-systolic volume; HR: heart rate; LVEF: left ventricular ejection fraction; NS: not significant.

Table 2. General baseline and stress characteristics. Group 1A vs. Group 1B.



CR: Contractile reserve; LVEF: Left ventricular ejection fraction.

Fig. 1. Contractile Reserve and Event Free Survival. Group 1 vs. Group 2.

As expected, patients with decreased CR assessed by LVEF had a worse prognosis. But within the group with LVEF still-preserved CR, the assessment of CR by elastance made it possible to identify two groups with different evolution, worse in those with decreased CR by elastance assessment.

The ABCD protocol proposed by Picano et al (10,11) integrates several parameters to be evaluated during the performance of a Stress Echo, through physical or pharmacological stress. The analysis of segmental motility or Asinergies (A) is only one of the variables to consider, to which is added the evaluation of B lines by means of lung echo (B), the evaluation of CR (C), and coronary reserve by measuring the behavior of the velocities in the distal anterior descending artery with pulsed Doppler (D). All these aspects are important for a comprehensive evaluation of cardiovascular function, not only in ischemic heart disease but also in other pathologies (12)

In an exhaustive patient assessment, CR measurement is one of the main parameters that we must take into account when analyzing the Stress Echo results. Although traditionally analyzed by the LVEF increase during the stress phase, this method has two important limitations: its strong dependence on loading conditions and the high intra- and inter- observer variability. Another method of measurement proposed is through the behavior of elastance, which has been validated in previous studies. (13,14) Normally, during stress, an increase in SBP is observed together with a decrease in indexed ESV, so that the relationship between the two doubles during the Stress Echo. It should be noted that other cut-off values are used in studies with vasodilators (a value >1.1 is considered normal), since the behavior of SBP and ESV is different.

Elastance reflects the intrinsic contractile state of the left ventricle, less dependent on loads. This measurement incorporates 2 recognized prognostic markers, a low increase in SBP during exercise and/or a smaller decrease in indexed ESV, which are associated with a worse prognosis and higher mortality. Previous studies suggest that this measurement could have greater sensitivity than the one assessed by LVEF, and could detect a group of patients at higher risk. (15,16)

In our study, we found 62.8% of patients with preserved LVEF and low elastance, a figure slightly higher than that described by T Bombardini et al. which refers this discrepancy in about 40% of patients. (5)

Under normal conditions, the end-diastolic volume of the ventricle has a slight increase at low exercise load, and then decreases at maximum effort to similar levels to those at rest, so that the increase in LVEF occurs fundamentally at the expense of the decrease in ESV. It is known that the EDV has no real influence on the calculation of the ventricular elastance, although it does on the LVEF. (17)

Experimental data suggest that ESV is less affected by loading conditions, especially preload, and its correlates with both resting and exercise systolic blood pressure. (18)

A study by Turakhia et al described in 934 patients with known coronary artery disease that those who had a reverse behavior of the left ventricle ESV with exercise had a higher incidence of cardiovascular events during follow-up, even in patients without ischemic behavior, like was observed in our work. (19)

We consider that the evaluation of ventricular volumes behavior should be done in all constraints (pharmacological and exercise), either by measuring the ventricular diameters or direct estimation through

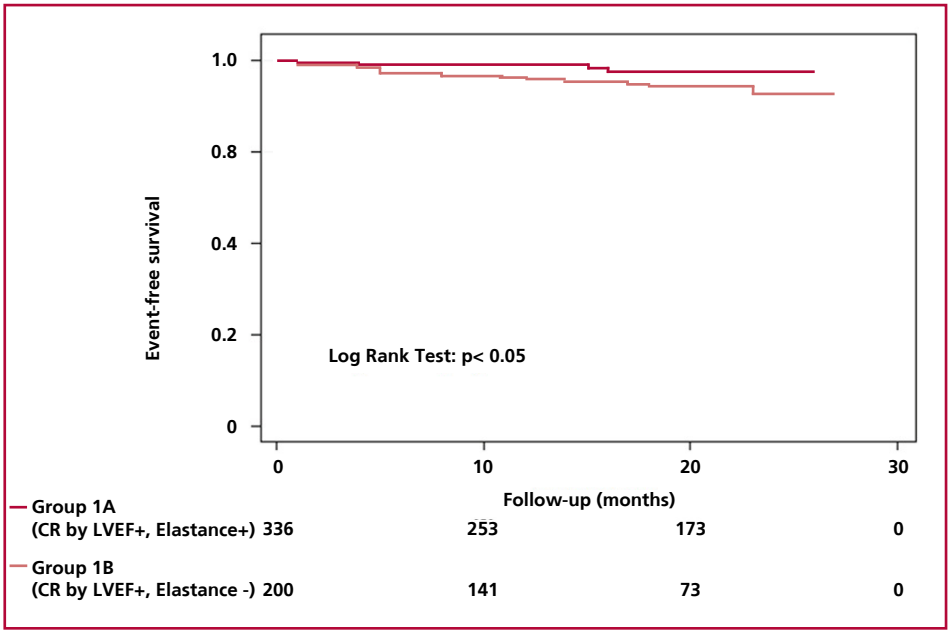


Fig. 2. Contractile Reserve and Event Free Survival. Group 1A vs. Group 1B.

CR: Contractile reserve; LVEF: Left ventricular ejection fraction.

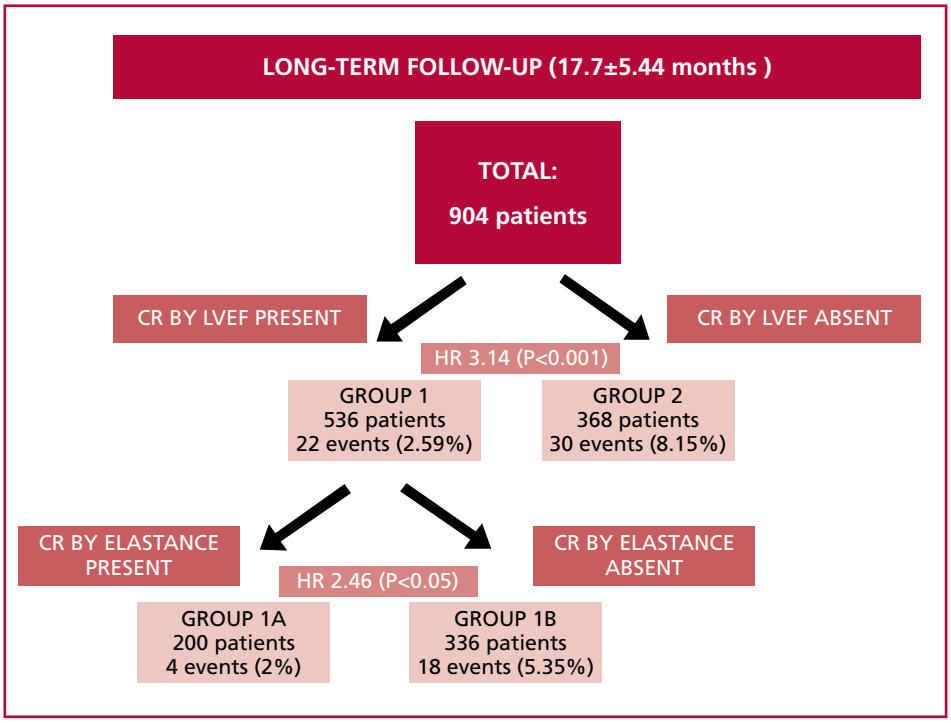


Fig. 3. Long term outcomes.

CR: Contractile reserve; LVEF: Left ventricular ejection fraction.

the Simpson method. It must be considered that an increase of 10 ml in ESV at maximum effort is associated with a 15% increase in the probability of serious events during follow-up. (19)

The determination of ESV is simpler than measuring LVEF, which needs to add the measure of EDV, so the error probability increases.

It is noteworthy that in an analysis carried out by our group, which has a lot of experience in measuring ventricular volumes semi-automatically, CR evaluated by elastance was not associated with the sufficiency of the ergometric test, so it is a useful parameter even in patients with poor exercise capacity or treated with beta blockers. (20)

We can conclude that a stress study can be defined as negative for myocardial ischemia when performing segmental motion analysis, but another parameters, such as ventricular elastance, allow adding additional prognostic information of great value.

Clinical Implications

Compared with the isolated measurement of CR by LVEF, ventricular elastance may be a more sensitive and accurate indicator of contractile reserve, less affected by load conditions and heart rate (Bowditch Treppe effect), reflecting the intrinsic contractility of the left ventricle during the exercise.

Our work shows that in addition to these pathophysiological advantages, its determination, which is very simple and does not require extra study time, has an impact on outcomes during patient follow-up; so its routine evaluation is suggested during Stress Echo studies. (Figure 3).

Limitations

The study was retrospective and single center.

We did not obtain, in the follow-up, the anatomical correlation by coronary angiography or computed tomography angiography, in those patients who had clinical events.

Finally, a small group of patients were evaluated under anti-ischemic medication, which can reduce the presence of contractile abnormalities during stress.

CONCLUSIONS

Decreased CR evaluated by ventricular elastance during a Stress Echo negative for myocardial ischemia and adequate behavior of the LVEF during exercise, allowed to identify a subgroup of patients with worse long-term prognosis.

Conflicts of interest

None declared.

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

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