

PROGNOSTIC VALUE OF STRESS ECHOCARDIOGRAPHY

Gerardo Manuel Marambio

Physician of the Cardiology Service of the Dr. Cosme Argerich Hospital for Acute Diseases

Different studies have shown the diagnostic accuracy of stress echocardiography in coronary artery disease, and in recent years, since the improvement in the quality of the images obtained with new echocardiographs, has become a diagnostic method widely used in our country and all over the world. This diagnostic method enables the evaluation of heart function in basal conditions, during and after challenge or stress, which could be physical exercise or pharmacological, with dobutamine and dipyridamole being the most commonly used drugs. The diagnosis of myocardial ischemia is based on the appearance, with the challenge, of new abnormalities of segmentary parietal motility or worsening of segmentary abnormalities already existing in basal conditions. Table 1.

Table 1: Diagnostic criteria of ischemia or myocardial necrosis in echocardiography with stress.

Segmentary motility in rest	Segmentary motility with challenge	Diagnosis
Normal	Normal or hyperkinesis	Normal or absence of ischemia
Normal	Hypokinesis, akinesis, or dyskinesis	Ischemia
Hypokinesis	Akinesis	Ischemia
Akinesis	Akinesis	Necrosis
Akinesis	Dyskinesis	Necrosis
Akinesis	Hypokinesis or normal	Viable

Besides diagnostic usefulness, the information obtained with stress echocardiography has a great clinical usefulness to define the prognosis of cardiac events, which may be even more important than the diagnostic capacity of the method.

Exercise is the challenge modality of choice in patients that can make physical exercise, due to a lower incidence of complications, and all the prognostic information, widely known and

validated, provided by the ergometer test. In patients with limitations to perform physical exercise, drug challenges that increase myocardial oxygen demand, such as dobutamine, or that produce coronary steal by coronary vasodilation, such as dipyridamole, are an excellent alternative.(1)

Different parameters obtained from stress echocardiogram have shown to have prognostic value: left ventricular systolic function in rest, the ischemic amount or extent of segmentary parietal motility alterations with stress, end systolic volume and the presence or not of myocardial viability. The compromised coronary territories, exercise load (mets), or the pharmacological dose at which myocardial ischemia appears, also have prognostic implications, as well as the time required for the affected segments to recover. Anti-ischemic therapy decreases the sensitivity of the method, but the development of myocardial ischemia under treatment entails a greater risk of events.

The left ventricular systolic function can be evaluated in a semiquantitative manner, estimating ejection fraction through the Simpson method, or subjectively, classifying it into normal, or with mild, moderate, or severe impairment.

It is possible to semiquantify ischemic amount through the parietal motility index, which is obtained in the following manner: the left ventricle is divided into 16 segments according the recommendations of the American Society of Echocardiography and each segment receives a number according to the subjective impression of the operator: normal=1, hypokinesis=2, akinesis=3, dyskinesis=4, and aneurysm=5, the values assigned to each segment are added, and this value is divided by the number of evaluable segments (usually 16). With this index, an analysis is obtained not just of the number of affected segments, but the degree of ischemic compromise presented by each segment.

In table 2, the different parameters that have shown a prognostic implication in stress echocardiography are summarized.(2)

Table 2: Parameters with prognostic implication in stress echocardiography.

Risk parameter	Low risk (<2% of events per year)	High risk (>20% of events per year)
Pharmacological dose or exercise capacity (Mets)	High	Low

Ejection fraction in rest	>50%	<40%
Anti-ischemic therapy	Absent	Present
Coronary territory	Cx or right coronary artery	Anterior descending artery
Parietal motility index	Low	High
Recovery	Rapid	Slow
Alterations of basal parietal motility or post-stress	Homozonal	Heterozonal
Increase of post-stress end systolic volume	No	Yes

The value of stress echocardiography to predict coronary events in a long term has been evaluated in different clinical situations and different subsets of patients, from those with suspicion of coronary artery disease, to patients with myocardial infarction, old or recent, from those who present just coronary risk factors such as hypertension or diabetes, to those patients with prior myocardial revascularization (coronary angioplasty or surgery), in women and even the risk of peri-operative cardiac events of patients that will receive vascular or non-cardiac surgery.

Precisely, this time we will analyze the prognostic value of stress echocardiography to predict cardiac events in different clinical situations.

Prognostic value of normal stress echocardiogram

Individuals with normal stress echocardiogram, defined as the absence of abnormalities of parietal motility in rest and post-challenge (exercise, dobutamine, or dipyridamole) have a very low incidence of cardiac events.

In a study that included more than 3,000 patients, in whom stress echocardiogram was performed (exercise or dobutamine), it was observed that the incidence of cardiac events (myocardial infarction or sudden cardiac death) in patients with normal stress echocardiography was approximately 0.8% per year. These patients were divided into three subsets according to the pre-test probability of CAD (low<15%, intermediary 15% to 85%

and high >85%) and the incidence of events was less than 1% per year in the three subsets when the study was normal.(3)

A meta-analysis that included 3021 patients of studies that evaluated prospectively the prognostic value of stress echocardiography with normal exercise, verified an annual incidence of myocardial infarction and/or death of 0.54% and unstable angina and/or revascularization of 0.95%; i.e. this negative predictive value (98.4%) confers stress echocardiography with normal exercise the capacity to identify patients at very low risk.(4)

Marwick TH et al, observed that after normal stress echocardiography with dobutamine, cardiac mortality was just 1% per year over the first 4 years of follow up.(5)

Gelejinse et al, studied 220 patients with precordial pain, and observed that stress echocardiography with normal dobutamine entailed an excellent prognosis, with an incidence of cardiac events of 0.4% per year. These patients underwent simultaneously a myocardial perfusion study, and normal stress echocardiography with dobutamine had a prognostic value comparable to normal myocardial perfusion.(6)

Finally, stress echocardiography with normal dipyridamole also implies a good prognosis, as was observed among others by Picano et al, in a comparative study with dobutamine.(7)

Prognostic value of abnormal stress echocardiogram

Abnormal stress echocardiography confers a risk of infarction or sudden cardiac death 5 times greater than normal stress echocardiography, 4% vs 0.8% per year. When the patients are divided in groups of low, intermediary, or high pre-test probability of presenting CAD (including patients with infarction and/or prior revascularization in the last group), a normal stress echocardiography implies a risk <1% in any of the groups, while an abnormal study defined a group with bad prognosis, increasing the incidence of events 3.4, 3.9, and 5 fold respectively in each group. In the patients with low pre-test probability, the severity of ischemia (high parietal motility index) is the greater predictor of events, while in the other 2 groups, a low ejection fraction, a high parietal motility index in rest, and history of CAD are also predictors of events. Moreover, stress echocardiography proved to have a prognostic value added to other variables such clinical symptoms (chest angina), clinical history (heredo-familial history, prior infarction, etc.) and mostly, ergometer variables.(3)

Olmos L et al, observed that abnormal exercise stress echocardiography due to the development of ischemia, entailed a worse evolution in a long term, with a prognostic value comparable to myocardial perfusion study with Thallium-201, and that a post-stress parietal motility index greater or equal to 1.4 was the main predictor of a bad prognosis.(8)

Even when a good exercise capacity in ergometer test (defined as >5 Mets in women and >7 Mets in men) is considered as a good prognosis factor, the development of abnormalities of parietal motility (ischemia) in these patients entails a greater incidence of events, mostly when they have an enough magnitude to cause an increase or no change in end systolic volume.

Likewise, abnormalities in motility in rest and the presence of echocardiographic signs of ischemia (variation of parietal motility index with stress) indicate a worse evolution, even in patients with completely normal ergometer tests.(9-10)

In the studies with Dobutamine, also the abnormalities of motility in rest, the development of ischemia (mostly the high percentage of ischemic segments or ischemic amount) and the increase of end systolic volume with stress have prognostic value. The development of ischemia implies a greater risk of myocardial infarction, while the presence of abnormalities in parietal motility in rest implies a greater risk of sudden cardiac death. The ischemic threshold also indicates risk and when the development of ischemia is observed with low heart rates in patients that do not receive beta blockers (HR<120 bpm or <76% of the heart rate expected for the age) or with low doses of dobutamine, it determines a greater risk of events. About the latter, that a study has a greater diagnostic sensitivity does not imply a greater prognostic accuracy, which could be observed with the addition of atropine, but with a variation in the parietal motility index <0.37 does not imply a greater risk of cardiac death than a normal dobutamine study.(2-11)

Also, dipyridamole allows an effective risk stratification on the basis of the presence, moment, severity, and extent of the induced ischemia. Especially, the extent and severity of induced left ventricular dysfunction are the most important predictors of sudden cardiac death. The patients that developed myocardial ischemia at low doses and/or a variation of parietal motility index >0.37 have a greater risk of sudden cardiac death than the patients with ischemia at high doses and/or variation of parietal motility index <0.37.(7)

Just as with the diagnostic capacity, positive tests of stress echocardiography with exercise, dobutamine or dipyridamole have a similar accuracy to stratify the risk of coronary events and the different parameters of stress echocardiography that entail a greater risk, are applied to any of the challenges.(12)

Currently, the prognostic value of stress echocardiography is clear, and it could be even more important than coronary angiography findings. Recently, From A et al, observed that the patients that presented abnormal stress echocardiography and angiographically normal coronary arteries or with <50% of obstruction (called false positives of stress echocardiography) show a similar risk of death to patients with abnormal stress echocardiography and >50% of obstruction (called true positives). This study is retrospective, and it shows important limitations, but it leads to performing other studies that would confirm these findings, and warns to pay more attention to these “false positives”, being more thorough to control coronary risk factors.(13-14)

Post-acute myocardial infarction prognostic value

In the acute stage, risk stratification in patients that survive acute myocardial infarction has the goal of identifying those patients whose prognosis can be improved with invasive diagnostic methods and coronary intervention, as well as those that only require medical treatment.

Ischemia and residual systolic function are the main determinants of post-acute myocardial infarction prognosis, and stress echocardiography, exercise or pharmacological, can be used to evaluate both prognostic factors as well as the presence of viability or contractile reservoir.

Although an impaired residual systolic function implies a poor prognosis, it is widely known that the impairment present in the first days of infarction can recover spontaneously in the first weeks or months post-infarction, since the recovery of the stunned myocardium.

Stress echocardiography with dobutamine at low doses (<10 gammas/kg weight/min) can identify a viable or stunned myocardium in the first week after acute myocardial infarction from the verification of an improvement in motility in dysfunctional myocardial segments (contractile reservoir). Pierard et al, are between the first to observe the contractile reservoir with dobutamine at low doses and that this group of patients recovers systolic function

spontaneously after infarction. Picano et al, evaluated the prognostic value of residual viability in patients treated medically with moderate to severe impairment of the global left ventricular systolic function (parietal motility index >1.6), detected by stress echocardiography with dobutamine at low doses conducted 12 ± 6 days post-myocardial infarction and observed that the patients that presented viability through this method (contractile reservoir) had a better evolution.(15,16)

However, although the presence of viability or contractile reservoir in stress echocardiography with dobutamine at low doses in post-infarction patients not complicated with significant impairment of systolic function, implies greater possibilities of spontaneous recovery, also relates to a greater incidence of non-hard cardiac events, like unstable angina.

On the other hand, it has been clearly proven that residual ischemia implies a worse prognosis, defining a group of patients that will benefit from a more aggressive treatment. Different studies have evaluated the prognostic capacity of stress echocardiography in their different challenge modalities and all of them have observed a greater annual incidence of events in patients with residual ischemia in comparison to patients without ischemia.(17)

When the patients present alterations in the basal electrocardiogram (left bundle branch block, repolarization alterations, permanent pacemaker, etc.) stress echocardiography with exercise offers clear advantages over ergometer test, besides allowing to locate the area and extent of compromised myocardium. When patients cannot perform exercise (prior stroke, osteoarticular problems, etc.) pharmacological challenges are a very useful option.

The studies made with stress echocardiography with dipyridamole in the first post-myocardial infarction days (<15 days) show that a positive study for the presence of residual ischemia implies a greater incidence in the first year of re-infarction, especially of fatal re-infarctions, in comparison to studies without residual ischemia.

Sicari et al, evaluated the value of ischemia induced by stress echocardiography with dobutamine in the first 15 days post-acute myocardial infarction and observed that in a follow up of approximately one year, the incidence of sudden cardiac death or myocardial infarction or unstable angina was greater in patients with ischemia in comparison to those without ischemia and that parietal motility index in maximal doses and remote ischemia (coronary territory different from the artery related to infarction) were the best predictors of events.(18)

Although in the study by Bigi et al, conducted with stress echocardiography with dobutamine, it was also observed that the change in parietal motility index between rest and peak stress (indicating residual ischemia) is an independent predictor of cardiac events, the main value of what was observed in this study, is the significant negative predictive value (90%) of stress echocardiography without ischemia in the early stage of infarction.(19)

In the previously quoted work by Picano et al, besides observing that residual viability in patients with systolic function impairment medically treated was a good prognostic factor, in these same patients, the presence of residual ischemia entailed a greater incidence of events and a poor evolution.

In conclusion, in the acute stage of infarction, the presence of ischemia in stress echocardiography implies a poor evolution with medical treatment and this group of patients should be considered for a more aggressive strategy with catheterization and revascularization. The prognostic significance of the presence of viability or contractile reservoir detected by stress echocardiography with dobutamine is controversial, since on one hand in patients with infarctions not complicated with impaired systolic function implies a greater incidence of non-hard cardiac events such as unstable angina, but on the other hand, it also entails greater chances of spontaneous recovery of systolic function by recovery of stunned myocardium, which in patients with systolic function impairment, clearly implies a better prognosis.

Prognostic value in chronic coronary artery disease. Viability.

In risk stratification of coronary events in the stage away from myocardial infarction, in chronic CAD, and mostly in left ventricular dysfunction with ischemic origin, stress echocardiography in any of its forms has a major role.

When the interest is on detecting only the presence of ischemia, as is the case of patients with good or slightly impaired systolic function, stress echocardiography with exercise has clearly proven to have a great prognostic value, and should be the modality of choice for its lower cost and lower incidence of severe complications.

Now, when the evaluation is to be made in patients with left ventricular systolic dysfunction (moderate to severe global systolic function impairment), stress echocardiography with

exercise could be of value to detect ischemia, but stress echocardiography with dobutamine is more useful, since it not only allows detecting the presence of ischemia, but it also enables detecting myocardial viability.

Myocardial viability is the capacity of the dysfunctional myocardium to recover spontaneously or after revascularization. The term viability suggests the potential to improve systolic function and it implies the presence of the stunned (it may recover spontaneously) and/or hibernated muscle (it requires revascularization to recover). Distinguishing the viable muscle from the non-viable one using stress echocardiography with dobutamine is based on the premise that viable myocardium improves motility and parietal thickening in response to beta adrenergic stimulus. Viability can be observed in stress echocardiography with dobutamine with an improvement of motility and parietal thickening at low doses, and in this case we speak of contractile reservoir, but the parameter with greatest predictive power of recovery after revascularization is biphasic response (improvement with low doses and new impairment with high doses, >20 $\mu\text{g/kg/min}$). This biphasic response suggests hibernated myocardium, irrigated by coronary artery that presents significant stenosis. The sensitivity of stress echocardiography to predict a recovery after revascularization ranges between 74% and 88% and specificity ranges between 73% and 90%, and comparatively with other techniques, such as radioisotope imaging, is a little less sensitive but more specific. (20,21)

Patients with significant systolic function impairment and a significant amount of viable and/or ischemic myocardium ($>25\%$ of the left ventricle) have a high probability of improving systolic function and the prognosis after revascularization in comparison to patients with extensive scar and no viability. It is also known that patients with ischemic and/or viable myocardium have a worse prognosis with medical treatment, and therefore, should be considered for revascularization.

In a meta-analysis that included studies with different diagnostic techniques (among them stress echocardiography with dobutamine) to evaluate viability in patients with moderate to severe systolic function impairment, and that evaluated the evolution with medical treatment vs revascularization, it was observed that in patients with viability, revascularization reduced annual mortality in almost 80% in comparison to patients treated medically (3.2% vs 16%),

while patients that did not present viability, did not show differences either, regardless of whether they had undergone revascularization or if they had received medical treatment.(22)

Prognostic value in revascularized patients

The capacity of stress echocardiography with exercise or drugs to detect restenosis subsequent to coronary angioplasty or coronary bypass occlusion after CABG, has been verified in different studies.(23,24)

The patients that present symptoms in the first months after coronary angioplasty, are generally studied again with coronary angiography because of the high possibility of restenosis, but asymptomatic patients can be evaluated by non-invasive functional tests.

According to the guidelines of the American College of Cardiology/American Heart Association, stress tests are recommended after revascularization only for patients with recurrent symptoms that suggest ischemia (Class I) or as part of cardiac rehabilitation (Class IIa). However, the symptoms after revascularization are commonly atypical and may not be considered secondary to restenosis or coronary bypass occlusion.(25)

Different studies have verified the capacity of stress echocardiography in any of their modalities to predict the development of symptoms secondary to post-angioplasty coronary restenosis.(26,27)

Bountiukos et al, evaluated the prognostic value of stress echocardiography with dobutamine in more than 300 patients previously revascularized by angioplasty or surgery. In an average follow up of 24 months, 13% of patients died and 30% had some coronary event (cardiac death, non-fatal infarction or new late revascularization) and observed that ischemia induced with dobutamine had an incremental predictive value of cardiac events.(28)

Arruda A et al, evaluated the prognostic value of exercise stress echocardiography in patients with prior CABG. In an average follow up of 2.9 years, post-strain abnormalities of end systolic volume, ejection fraction and parietal motility index were independent predictors of cardiac events, adding predictive value to basal clinical and echocardiographic variables and ergometer variables.(29)

As we see, beyond diagnostic capacity of coronary restenosis or coronary bypass occlusion and the capacity to locate the compromised coronary territory, stress echocardiography from

their high risk parameters is capable of predicting a poor evolution in revascularized patients, clearly collaborating in therapeutic choice.

Role in risk stratification prior to non-cardiac surgeries

The cardiologic evaluation of patients that will undergo non-cardiac surgery has as its goal to identify those who are in risk of major cardiovascular complications. There are clinical predictors of major risk and surgeries that entail a greater risk than others.

In those patients that present clinical risk predictors such as advanced age, chest angina, recent myocardial infarction or heart failure, stroke, diabetes, or renal failure, it is necessary to conduct an intensive cardiovascular evaluation.

Although specific factors of the patient are more important to predict the cardiac risk in non-cardiac surgeries, the type of surgery cannot be ignored.

Major vascular surgery, aortic or peripheral vascular, is the type of surgery with major risk, and where the role of non-invasive tests has been studied more in depth. The incidence of peri-operative cardiac complications in these patients is associated to the prevalence of coronary artery disease. The prevalence of severe coronary artery disease is 36% of patients who underwent abdominal aortic aneurysm surgery, in approximately 28% of patients under infrainguinal revascularization and only 6% of all patients with vascular disease have angiographically normal coronary arteries.

The objective of pre-operative non-invasive tests is providing information about 3 markers of cardiac risk: left ventricular dysfunction, myocardial ischemia, and cardiac valves abnormalities, all major determinants of peri-operative adverse events. All these markers can be evaluated during stress echocardiogram in any of its modalities.

The ergometer test is, because of its low cost and high negative predictive value, the method of choice to detect myocardial ischemia and moreover, provides an estimation of functional capacity that is another significant predictor of peri-operative events. But although it has a high negative predictive value (98%), i.e. a normal study predicts virtually the absence of complications, it has a very low positive predictive value (10%), i.e. low capacity to predict cardiac complications. Besides, there is a great population of patients that present difficulties to interpret or perform an ergometer test, like those with basal electrocardiographic alterations

(branch blocks, non-specific ST alterations, etc.) or osteoarticular or muscular problems, intermittent claudication, etc. In this population of patients, the addition of images has real value: exercise stress echocardiography in patients with basal electrocardiographic or pharmacological alterations in patients that cannot perform exercise.

Stress echocardiography with exercise or drugs (dobutamine or dipyridamole) has been widely used to evaluate peri-operative cardiac risk. This method combines information about ventricular function in rest, abnormalities in cardiac valves, and the presence and/or the extent of myocardial ischemia.(30)

A meta-analysis compared the prognostic accuracy of 6 different diagnostic methods to predict peri-operative cardiac risk in patients under major vascular surgery: Holter electrocardiographic monitoring, ergometer test, radioisotope ventriculography, myocardial perfusion with radioisotopes, stress echocardiography with dobutamine and stress echocardiography with dipyridamole. The conclusions of this study were that both Holter monitoring and radioisotope ventriculography should not be used as a routine in pre-operative evaluation due to their low sensitivity and that stress echocardiography with dobutamine showed a better prediction of cardiac events in regard to other methods, although it was just statistically significant in regard to myocardial perfusion with radioisotopes. Moreover, it was observed that the predictive value of any of the stress tests has a significant negative predictive value (90% to 100%), although stress echocardiography adds information about the state of the cardiac valves, and left ventricular systolic function in rest.(31)

Another, more recent meta-analysis that compared stress echocardiography with myocardial perfusion studies with radioisotopes in pre-operative evaluation of any type of surgery, observed on one hand, that stress echocardiography is superior to myocardial perfusion with radioisotopes to predict peri-operative cardiac events, and on the other hand, the significance of the ischemic amount, since a moderate to severe ischemic defect in any of the 2 techniques with positive tests for myocardial ischemia, should be considered of increased risk for peri-operative cardiac events and be managed with monitoring and maximal medical therapy, and the patients with moderate to severe ischemic amounts should be studied with coronary angiography and if possible, revascularized previously to non-cardiac surgery.(32)

To conclude, the records on marked ischemia induced with stress echocardiography, has a strong independent prognostic value to identify patients in high risk of presenting peri-operative cardiac complications, who could benefit from CABG prior to surgery, mostly if this is a major vascular surgery, and on the other hand, the absence of ischemia is associated to a very low incidence of cardiac events, enabling a safe procedure.

Prediction of cardiac events in different populations

The patients with diabetes are a group with high incidence of cardiovascular disease, of coronary artery events, and silent ischemia, as well as having a greater morbi-mortality after myocardial infarction in comparison to non-diabetic patients. In this population, exercise stress echocardiography positive for myocardial ischemia provides an independent incremental prognostic value, even more when the ischemic alterations are present in different coronary territories, and a normal stress echocardiography predicts a very low incidence of cardiac events. For diabetic patients that cannot perform exercises, both stress echocardiography with dobutamine or with dipyridamole have shown to have independent predictive value for cardiac events.(33-36)

The incidence of CAD in women is increasing as years advance, and the question has arisen about whether stress diagnostic studies have the same prognostic value as in men. Different studies have shown that both stress echocardiography with exercise and the pharmacological tests are independent predictors of cardiac events in women just as in the male sex, even when the incidence of events is still greater in men.(37,38)

In patients with right bundle branch block, with permanent pacemaker, and mostly with left bundle branch block, and stress echocardiography has proven to be useful both for the diagnosis and to predict the prognosis of CAD.

Hypertension is strongly associated with CAD, and non-invasive evaluation in this population of patients could be highly difficult with simple ergometer test, which presents a low specificity, since they generally present basal electrocardiographic alterations. The stress echocardiography in any of its modalities has shown, in this population of patients, that it has an independent prognostic value, incremental to clinical data and to left ventricular mass index.

Conclusion

Stress echocardiography in any of its modalities is a very useful technique for the prognostic evaluation of the patients with suspicion and/or known CAD, particularly in those with basal electrocardiogram alterations and those with disability or limitations to perform exercise. The patients with normal stress echocardiography have a very low incidence of cardiac events, a very good prognosis, and do not require a greater diagnostic evaluation, while patients with extensive abnormalities of parietal motility subsequent to stress, have a high risk of death and myocardial infarction and coronary angiography with subsequent revascularization should be evaluated. Also, myocardial viability could be defined with stress echocardiography with dobutamine and its presence in patients with left ventricular dysfunction predicts the improvement of systolic function subsequent to revascularization.

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