Noninvasive assessment of coronary artery disease: the role of stress echocardiography

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Echocardiography combined with either exercise or pharmacological stress is a widely used method for the noninvasive assessment of coronary artery disease. This is due to the high diagnostic accuracy that does not differ substantially among the various stress modalities. In addition, stress echocardiography has a useful role in risk stratification of patients with known or suspected coronary artery disease. In particular, evidence of inducible ischemia is predictive of an unfavorable outcome, whilst its absence is associated with a very low risk of future cardiac events. These findings have strong implications in clinical decision-making.

One of the main characteristics of the echographic marker of ischemia is that it is significantly more specific than the electrocardiographic one. The higher specificity of stress echocardiography translates into increased prognostic value as compared to exercise electrocardiography. Nevertheless, exercise electrocardiography has a very high negative predictive value. Moreover, compared to stress echocardiography it is safer, simpler, less costly and requires no specific competence. Based on these data, exercise electrocardiography remains the cornerstone of the noninvasive evaluation of coronary artery disease. Stress echocardiography, on the other hand, is particularly useful in those cases when exercise electrocardiography is not feasible, non-interpretable (owing to the presence of left bundle branch block or of a pacemaker or of other electrocardiographic baseline abnormalities), or when it gives inconclusive data, or a positive result at an intermediate or high workload (in such cases, precise knowledge of the site and extension of ischemia can be of crucial importance in deciding between conservative and aggressive treatment), as well as in cases in which ischemia during the test is frequently a false positive response, as in hypertensive patients, in women and in all cases of left ventricular hypertrophy.

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Introduction

Stress echocardiography relies on the induction of ischemia by means of different mechanisms that may either act by enhancing myocardial oxygen consumption (exercise, dobutamine, arbutamine, pacing), or produce an inappropriate arteriolar vasodilation with subsequent inadequately distributed flow (dipyridamole, adenosine), or result in coronary artery spasm (ergonovine)[1]. Although exercise should be considered the ideal stress modality, in the light of the fact that it reproduces a physiological condition[2], the inability to perform physical exercise by some patients has facilitated the diffusion of alternative tests such as pharmacological stress with dipyridamole[3] and dobutamine[4].

Diagnostic accuracy

Exercise echocardiography. Imaging of the heart during exercise adds to the accuracy of the electrocardiogram, with an overall sensitivity ranging from 78-97% and specificity from 64-100%[5-8] that may partly be accounted for by the choice of the protocol. Registration during the recovery phase may be facilitated by better imaging quality but counterbalanced by the possible disappearance of minor regional wall motion abnormalities, especially in case of single-vessel disease. On the other hand, imaging at peak exercise may provide more accurate recognition of disease when imaging quality is favorable. With regard to single vessels, the sensitivity is best for the left anterior descending coronary artery (77%) as compared to the right coronary artery (70%) and the circumflex coronary artery (67%)[9]. However, sensitivities as low as 45% have been reported for the circumflex coronary artery[10].

Pharmacological stress echocardiography. Failure, due to inadequate exercise capacity as well as orthopedic, vascular or neurologic problems, to achieve adequate

levels of stress during exercise reduces the sensitivity of the test. In such cases, pharmacological stressors represent a valid alternative which maintains a high diagnostic value that does not substantially differ among the various stress modalities. A recent meta-analysis of seven studies comparing dipyridamole and exercise stress echocardiography in a series of 467 patients showed a higher specificity for the pharmacological stressor (93 vs 82%, p < 0.05) and a better sensitivity for exercise (80 vs 72%, p < 0.05), with comparable diagnostic accuracy (77 vs 80%, p = NS)[11]. Similar results have been observed in a meta-analytic comparison of the two most popular pharmacological stress tests, i.e. dipyridamole and dobutamine, conducted on 818 patients. The higher sensitivity of dobutamine (77 vs 71%, p < 0.05) was counterbalanced by a lower specificity as compared to dipyridamole (87 vs 93%, p < 0.05) so that the diagnostic accuracy of the two methods was not substantially different (80 vs 77%, p = NS)[12].

International guidelines suggest that pharmacological stress echocardiography might be best accomplished using adrenergic stimulants and a superiority of adrenergic over vasodilator stress has been quoted in patients with single-vessel disease[13-16]. Nevertheless, atropine administration during dipyridamole stress is capable of inducing a step-up in sensitivity especially in patients with single-vessel disease[17]. Our experience in stress echocardiography suggests that dipyridamole and dobutamine are complementary and that both should be routinely used in every stress echo laboratory in order to obtain the best individualized information. Important reasons for preferring one test to the other should be the contraindications inherent to each test and the specific information that is expected from the examination. So, in the arrhythmic patient dipyridamole could be the preferred stressor, while the evaluation of viability calls for the use of dobutamine as the first choice stressor.

Other types of stressors. Pacing stress echocardiography has been used as an alternative to exercise or pharmacological stimuli, especially in association with transesophageal imaging, with a global accuracy in detecting coronary artery disease ranging from 83 to 93%[18-20]. Ergonovine stress echocardiography has also been reported as an accurate method for the noninvasive diagnosis of variant angina, with a sensitivity and specificity higher than 90%[21,22].

Prognostic value

The availability of echocardiographic equipment in all medical centers has been a factor of paramount importance for the diffusion of stress echocardiography as a noninvasive technique in the diagnostic work-up of ischemia, especially in the light of its limited costs and resource consumption. In spite of its diffusion to smaller centers with (possibly) less expertise in the evaluation

of echocardiograms during stress, it is quite reassuring to observe that, even in these settings, stress echocardiography maintains its prognostic power. In a series of 1082 patients with known or suspected coronary artery disease, the presence of ischemia during pharmacological stress echocardiography was a powerful independent predictor of cardiac death or combined cardiac death and infarction[23]. Particularly appealing is the very high negative predictive value of the test that is demonstrated by a 99% survival and 97% infarction-free survival rate at 3 years of follow-up[23]. Stress echocardiography results can therefore heavily impact the decision-making process, allowing a selective use of invasive procedures, with potentially favorable economic and logistic consequences, especially in peripheral centers. In the same aforementioned article, 71% of patients with and 13% of patients without inducible ischemia were submitted to coronary angiography, while revascularization procedures were performed in 37% of ischemic and in 3% of nonischemic patients[23].

In spite of the baseline low risk profile, stress echocardiography maintains a high prognostic value even in the minor forms of coronary artery disease such as single-vessel disease. Furthermore, the test has been shown to efficaciously predict which patients would benefit most from coronary revascularization. In a series of 754 patients with single-vessel disease, ischemia during stress echocardiography was the only variable independently correlated with hard events (odds ratio-OR 2.9) occurring in patients maintained on medical therapy[24]. Moreover, in the group of patients who were revascularized early after the test, a significant prognostic amelioration was seen only in those who had pre-procedural inducible ischemia, whilst in patients without ischemia the 4-year infarction-free survival rate was similar to that of nonischemic patients who were medically treated[24].

As for the prognostic implications of the different pharmacological stress modalities, a similar prognostic value has been reported for dipyridamole and dobutamine testing both in multicenter[25] and in single-center experiences[26,27].

The prognostic impact of stress echocardiography in patients recovering after an acute myocardial infarction has been extensively demonstrated[28-34]. In particular, the extension of the jeopardized myocardium, expressed by the peak wall motion score index, represents the most powerful indicator of an unfavorable outcome[30]. On the contrary, the high negative predictive value of the test has been proposed as a strategic component in the early evaluation of patients with preserved left ventricular function and no signs of residual ischemia who are hence candidates for early hospital discharge[29,35]. Viability detection represents the other component of the prognostic assessment after an acute myocardial infarction, especially in patients with depressed ventricular function in whom the presence of inotropic reserve during dobutamine stress is associated with a higher

probability of survival[36]. Nevertheless, even in patients with mildly impaired function the interaction between ischemia and viability gives prognostically important hints and provides a useful framework for the noninvasive selection of those patients to be submitted to coronary angiography[37].

Safety issue

An important aspect of noninvasive testing is represented by the complication rate[38,39]. A recent study[40] referring about the experience of 63 different centers with a total number of more than 80 000 examinations, the complication rate for exercise, dipyridamole and dobutamine stress echocardiography were 1/25 213, 1/1256 and 1/412 exams respectively. Fatal events were observed in 6 cases, 5 of which during dobutamine (3 cases of heart rupture and 2 cases of ventricular fibrillation), and one during dipyridamole stress (a case of uncontrollable hypotension) with a fatal complication rate of 1/6524 for dobutamine and 1/23 876 for dipyridamole.

Comparison with exercise electrocardiography

In the light of data on safety, diagnostic accuracy and prognostic implications, it seems of utmost importance to verify the role of stress echocardiography as compared to exercise electrocardiography in the noninvasive evaluation of coronary artery disease. One of the main characteristics of the echographic marker of ischemia is that it is significantly more specific than the electrocardiographic one, as was observed in patients with chest pain, normal ventricular function and a negative history of coronary artery disease[41]. The higher specificity of stress echocardiography translates into increased prognostic value as compared to clinical and exercise electrocardiography data[41]. However, the performance of additional noninvasive tests should not be pursued in the presence of a negative exercise electrocardiography test in view of the high negative predictive value[41].

Therefore, there seem to be many reasons in favor of exercise electrocardiography as the first line test in the noninvasive evaluation of coronary artery disease. When compared with stress echocardiography, it is safer, simpler, less costly and requires no specific competence. In addition, it has a very high negative predictive value. On the other hand, a sizable proportion of patients referred for the diagnosis of coronary artery disease cannot perform exercise testing or else exercise submaximally owing to various reasons, including little motivation and orthopedic, vascular or neurologic problems. Moreover, sometimes the electrocardiogram is not interpretable (due to the presence of left bundle branch block or of a pacemaker or of other baseline abnormalities)[42], or gives ambiguous responses during the test, as in women[43], hypertensive patients[44] and in all cases of left ventricular hypertrophy[45]. In these clinical subgroups the increased value of stress echocardiography as compared to exercise electrocardiography seems particularly important.

Special clinical groups

Patients unable to exercise. In a consecutive series of 394 patients unable to exercise, pharmacological stress echocardiography was highly effective in discriminating between samples at low and high risk on the basis of the presence or absence of inducible ischemia. In particular, ischemia during the test demonstrated a high independent prognostic value for both cardiac death (OR 24) and hard events (OR 14) at follow-up[46].

Hypertensive patients. The issue of discriminating heart disease in hypertensive patients is of utmost importance, since coronary artery disease is the most frequent vascular complication of systemic hypertension[47]. Nevertheless, the diagnostic value of exercise electrocardiography and nuclear techniques has been very disappointing[44,48-50]. In this clinical population, stress echocardiography has provided particularly interesting results. Comparison of dipyridamole stress echocardiography and exercise electrocardiography in a series of patients with chest pain of unknown origin revealed a similar sensitivity for the two methods but a higher specificity for the imaging technique (92 vs 46%, p < 0.05)[51]. Similar results have been reported with dobutamine[52]: stress echocardiography was shown to be more specific than exercise electrocardiography (100 vs 29%, p < 0.005) with no significant differences in sensitivity between the two tests. In the comparison between dobutamine stress echocardiography and perfusion scintigraphy, the diagnostic sensitivity of the two techniques was similar but the specificity was higher for stress echocardiography (83 vs 67%, p = 0.05)[53]. In a study undertaken to compare perfusion scintigraphy, dipyridamole and dobutamine stress echocardiography in hypertensive patients with a positive exercise test, dobutamine echocardiography most accurately assessed organic coronary artery disease[54]. However, the stress protocols used in that study did not include atropine co-administration. In a very recent paper the use of atropine strongly enhanced the diagnostic power of vasodilator stress in hypertensive patients with a positive exercise test[55]. As for the prognostic implications of stress echocardiography in hypertensives, in a cohort of 257 patients with a negative history for coronary artery disease and examined for chest pain, inducible ischemia during dipyridamole stress was an independent predictor of both the composite outcomes of cardiac death and infarction (OR 5.5) and spontaneous cardiac events (including hospitalizations for unstable angina) (OR 4.2)[56].

Women. Stress echocardiography is increasingly used in women for the diagnosis of coronary artery disease. In females, dipyridamole stress showed a sensitivity similar to that of exercise electrocardiography but its specificity (93 vs 52%, p < 0.001) and diagnostic accuracy (87 vs 62%, p < 0.001) were better[57]. Similar results have been obtained in the comparison between exercise echocardiography and exercise electrocardiography, with similar sensitivity but a higher specificity (81 vs 56%, p < 0.001) and diagnostic accuracy (81 vs 64%, p < 0.005) for the imaging method[58]. The prognostic value of stress echocardiography is high even in women. In a consecutive series of 456 patients with chest pain and without a previous history of coronary artery disease, ischemia at stress echocardiography independently predicted both hard (OR 27) and spontaneous cardiac events (OR 24)[59]. Moreover, compared to clinical and exercise electrocardiography data stress echocardiography was found to have an incremental prognostic value. When either hard or spontaneous cardiac events were primary endpoints, the global χ^2 value augmentation was greater than 200%[60].

Patients with left bundle branch block. In patients with left bundle branch block dobutamine stress echocardiography has demonstrated good diagnostic accuracy, independently of the coronary territory under study[61,62]. This is of particular importance considering that the diagnosis of ischemia in the anteroseptal wall represents the Achilles' heel of nuclear methods in these patients[63,64]. Moreover, myocardial ischemia by pharmacological stress echo showed a strong and independent power in the prediction of future hard events in left bundle branch block patients, providing a prognostic contribution that was incremental to that of clinical and resting echo findings in the group without previous myocardial infarction[65].

Patients undergoing vascular and nonvascular surgery. Patients undergoing vascular surgery represent a high risk group. Atherothrombosis is a very common condition encompassing the peripheral, cerebral and coronary circulation. Patients with coronary artery disease often have concomitant noncoronary atherosclerosis[66] and in 30-50% of the cases, patients with peripheral vascular disease have a significant coronary pathology[67]. Therefore risk stratification before surgery is a major issue. These patients are often unable to adequately perform exercise and pharmacological stress echocardiography represents an important alternative. Among patients with a clinically high risk profile, a high peak wall motion score index further selects those at increased risk and, by identifying those patients who may benefit from beta-blocker treatment[68] or in whom preoperative coronary invasive evaluation must be performed[69], helps in the decision-making process. Even in patients with known or suspected coronary artery disease evaluated before nonvascular surgery, dobutamine stress echocardiography better identified those patients at low, intermediate and high postoperative risk than clinical, electrocardiographic and resting echo parameters[70].

Conclusions

In conclusion, the first step of noninvasive evaluation of coronary artery disease should be exercise electrocardiography, able as it is to identify patients at very low risk in case of a negative result and those at high risk in case of a low workload positive result. In these situations, the information provided by stress echocardiography appears to be redundant and therefore useless. Stress echocardiography, on the other hand, is particularly useful in those cases when exercise electrocardiography is not feasible, non-diagnostic, non-interpretable, or when it gives inconclusive data, or a positive result at intermediate or high workloads (in this case, precise knowledge of the site and extension of ischemia can be of crucial importance for clinical decision-making), as well as in those cases where ischemia during the test is frequently a false positive response, as occurs in hypertensive patients and in women.

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