Risk stratification with pharmacological stress echocardiography in post-acute myocardial infarction patients

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(Ital Heart J 2001; 2 (4): 245-249)

Received November 9, 2000; revision received January 11, 2001; accepted January 25, 2001.

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The management of the patient surviving a myocardial infarction has important clinical implications. However, the approach to such patients is multifaceted and varies according to different factors: type of infarction (complicated versus uncomplicated) and type of methodology used for stratification [invasive versus non-invasive (ischemia-guided)] that in turn influence the outcome. Patients with a complicated myocardial infarction (severe ventricular dysfunction, early recurrence of angina, the presence of major life-threatening arrhythmias) appertain to a group at very high risk of future hard cardiac events and they should undergo coronary catheterization in order to assess the feasibility of a coronary revascularization which in turn may change the natural history of their coronary artery disease[1]. The main concerns arise when the clinician has to face patients with uncomplicated disease: they comprise roughly 80% of the survivors of a myocardial infarction and, in the first 6 months after the acute event, have an incidence of cardiac death ranging between 2 and 10%. Therefore these patients belong to the very low to intermediate risk groups. Among these patients, is it possible to identify those who are at higher risk and who would therefore benefit from an aggressive approach? In other words is it possible to lower their risk? And how may their risk be detected?

Pharmacological stress echocardiography and prognosis in patients recovering after an acute myocardial infarction: the results

If the major determinants of prognosis in post-acute myocardial infarction patients were the residual left ventricular function, the presence of inducible ischemia and eventually the presence of myocardial viability, pharmacological stress echocardiography would provide all the information needed by offering a rational trade-off between theory, practice and costs. The evidence regarding pharmacological stress echocardiography was obtained through large scale, multicenter, prospective, observational studies. Such studies overcome the major limitations of most available prognostic studies with specialized imaging testing: relatively small sample size and the need to include soft and subjective endpoints, such as revascularization procedures, in order to increase the power of prognostication. Moreover, many prognostic studies enrolled selected patient populations and were performed in highly specialized centers unlikely to represent the everyday clinical practice of most non-academic institutions. The picture provided is the realistic one of busy echocardiographic laboratories dealing with clinical questions and not virtual patients. The pharmacological stress echocardiographic response is not a binary (black or white) response, but positivity should rather be titrated according to space and time coordinates offering a wide spectrum of shades of gray[2]. A positive stress echocardiographic response associated with hypokinesis of two segments of the lateral wall after the high dose of dipyridamole carries a risk of cardiac death of 2 to 3% per year, whereas a positive response associated with akinesia or dyskinesia of six to eight segments in the territory of the left anterior descending artery after a low dose of dipyridamole is associated with a risk of cardiac death of 15 to 20% per year. Therefore, for

prognostic purposes the stratification of the ischemic response is even more important than its presence. In the Echo Persantine International Cooperative Study (EPIC)[3] which enrolled almost 1000 patients, the 1-year risk of cardiac death after an acute myocardial infarction was as low as 2% (n = 34) in patients with a negative response at dipyridamole stress echocardiography; it averaged 4% if the test was positive at high dose, and it was 7% in case of low dose positivity (Fig. 1). Moreover, this information is additive to that obtained with resting echocardiography; combining the two techniques, the stratification capability is higher ranging from a 2% risk for those patients without inducible ischemia and with moderate impairment of left ventricular function to an 11% risk for those patients with reduced resting left ventricular function and inducible ischemia (Fig. 2). Consistent with these data are the results of the Echo Dobutamine International Cooperative Study (EDIC)[4] in which almost 800 patients were evaluated early after a first acute uncomplicated myocardial infarction. The induction of remote ischemia was associated with an increased incidence of cardiac death and reinfarction (n = 37). The peak dobutamine wall motion score index, which provides an integrated assessment of the extent and severity of left ventricular dysfunction at peak stress and correlates to the extent and severity of the underlying coronary artery disease[2], was the strongest predictor of subsequent cardiac death. In addition, several studies have shown that the prognostic value of pharmacologically-induced ischemia is independent of and additive to that of clinical and exercise electrocardiography variables[5-7]. In a subproject of the EPIC study comparing the prognostic value of pharmacological stress echocardiography using dipyridamole versus exercise electrocardiography in 547 patients studied early after an uncomplicated myocardial infarction, the extension and severity of induced left ventricular dysfunction, identified by the delta wall motion score index, was the most important predictor of future spontaneous events (n = 85). When stratifying the positive response according to timing, severity and extension of ischemia, patients with a positive test at low doses and/or with a high delta wall motion score index were at higher risk of spontaneous events compared to those with a positive test at high doses and/or with a low delta wall motion score index[8]. For prognostic purposes, only two studies directly comparing perfusion scintigraphy versus two-dimensional echo dipyridamole stress imaging have been performed in patients evaluated early after an acute myocardial infarction. Both studies showed that in these patients perfusion defects are more frequent than wall motion abnormalities, but wall motion abnormalities are prognostically more meaningful than perfusion defects[9,10].

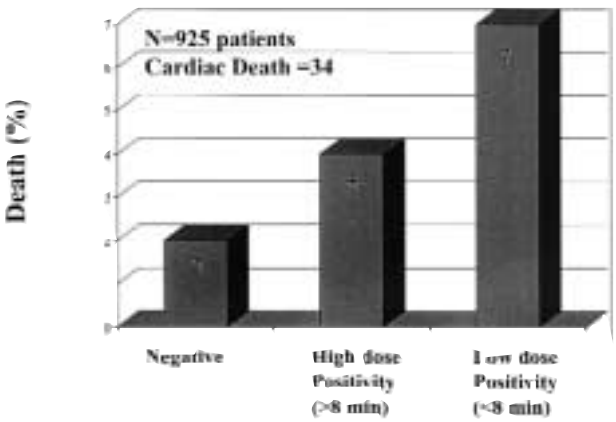

Figure 1. *Prognostic stratification of dipyridamole stress echocardiography early after an uncomplicated acute myocardial infarction. Histogram showing the incidence of death in three groups of patients: those with negative dipyridamole stress echocardiography results, those with high-dose dipyridamole stress echocardiography positivity, and those with low-dose dipyridamole stress echocardiography positivity.*

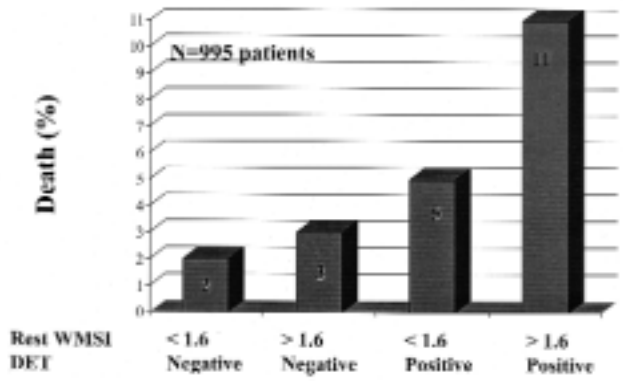

Figure 2. *Prognostic stratification of dipyridamole stress echocardiography (DET) early after an uncomplicated acute myocardial infarction. Combined effect of resting function and inducible ischemia (with stress echocardiography) on the incidence of mortality in early post-infarction (10 days after acute myocardial infarction). Follow-up 14.6 ± 10.2 months. WMSI = wall motion score index.*

The role of myocardial viability in risk stratification after an acute myocardial infarction

In patients evaluated early after a first acute uncomplicated myocardial infarction the presence of myocardial viability detected by dobutamine stress echocardiography is associated with an increased incidence of unstable angina (n = 61) but not with the occurrence of hard events[4]. When the prognostic significance of myocardial viability was evaluated in a population of 314 medically treated patients with moderate-to-severe global left ventricular dysfunction early after acute uncomplicated myocardial infarction, the presence and extent of myocardial viability identified as the inotropic reserve following low dose dobutamine was associated with a higher probability of survival[11]. Still, even in this set of patients the presence of inducible ischemia, identified by the wall motion score index at peak stress, strongly increased the prognostic power of myocardial viability at low dose dobutamine with a relative risk for the prediction of cardiac death of 14.9 (Fig. 3). The "para-

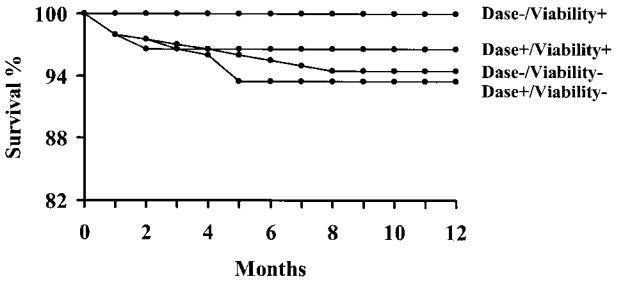

Figure 3. *Prognostic implication of ischemia and viability assessed early after an acute myocardial infarction in patients with resting dysfunction. Kaplan-Meier survival curves (considering only death as an endpoint) in patients stratified according to the presence or absence of echocardiographically assessed viability and ischemia at low and high doses of dobutamine respectively. Viability+ and viability- indicate the presence or absence of myocardial viability at low dobutamine doses respectively. Dase+ (dobutamine-atropine stress echocardiography) and Dase- (dobutamine-atropine stress echocardiography) indicate the presence or absence of myocardial ischemia at high dobutamine doses respectively. The best survival is observed in patients with low dose viability and no inducible ischemia; the worst survival is observed in patients without viability and with inducible ischemia.*

dox" of the impact of viability on prognosis in patients evaluated early after an acute myocardial infarction can be solved if one takes into account that viability can be both "good" (associated with a better outcome) and "bad" (associated with a worse outcome) depending on the patient under study and the outcome endpoint considered. Therefore, in patients recovering after an acute myocardial infarction, viability is good (associated with a better survival) in patients with bad ventricles who are aggressively treated, and viability is bad (with a greater probability of unstable angina) in patients with good ventricles, i.e. with a reasonably preserved global left ventricular function. Nonetheless, its prognostic weight appears to be negligible since it has no ability to predict hard endpoints such as cardiac death and besides its significance is obscured by the information provided by the presence of myocardial ischemia able to identify those patients at higher risk for death. In practical terms, we get the information during stress echocardiography but we do not use it. The only important subset in which myocardial viability has a critical meaning consists of those patients with severe baseline left ventricular dysfunction, with an extensive viability response at low doses and no inducible ischemia at high doses during pharmacological stress echo[11]. These patients have an excellent survival even when left on medical therapy, suggesting that even in patients with severe left ventricular dysfunction the prognosis can be substantially heterogeneous, and stress echo identifies a subset with a benign outcome, characterized by extensive viability and no ischemia (Fig. 3). It is also important to remember that the information provided by viability can also be obtained with low drug dose stress echocardiography not only with dobutamine but also with dipyridamole, as shown in patients evaluated early after acute myocardial infarction and chronic coronary artery disease[12-14]. The information obtained with low dose dipyridamole is as accurate as the one provided by low dose dobutamine in identifying viable myocardium early after acute myocardial infarction[15,16]. As recently shown by the VIDA (Viability Identification with Dipyridamole Administration) Study[17] which enrolled 307 patients with chronic severe left ventricular dysfunction, the viability identified by low dose dipyridamole is also an extremely powerful predictor of survival in patients with chronic severe left ventricular dysfunction undergoing revascularization.

Ischemia versus anatomically-guided revascularization: the role of stress echocardiography

The results of large scale, observational multicenter trials demonstrate the ability of pharmacological stress echocardiography to risk-stratify patients, identifying those who might benefit from ischemia-guided coronary revascularization. The natural history of this set of patients might be dramatically changed by revascularization interventions guided by physiologic testing. In the EPIC study, patients with an uncomplicated myocardial infarction who underwent coronary revascularization on the basis of a positive test had an 11-fold reduction in the risk of cardiac death. When the revascularization procedure was undertaken in the absence of stress echocardiography-inducible ischemia, the risk of death increased 3-fold[3]. These data are consistent with those of studies which used an ischemia-guided approach to revascularization after an uncomplicated myocardial infarction. The Danish Acute Myocardial Infarction investigators reported that when patients with inducible myocardial ischemia after thrombolysis for acute myocardial infarction were randomized to cardiac catheterization and revascularization versus conservative medical therapy, anti-angina medications were used less frequently and the incidences of unstable angina and of non-fatal reinfarction were lower among those assigned to the revascularization group[18]. In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital trial, 920 patients with a new non-Q-wave myocardial infarction were randomized to an early "invasive" strategy (routine coronary angiography followed by myocardial revascularization, if feasible) where the use of coronary angiography and myocardial revascularization was guided by the development of ischemia versus an early "conservative" strategy (non-invasive, pre-discharge stress testing with thallium scintigraphy and radionuclide ventriculography). The rates of death or of non-fatal myocardial infarction were significantly higher in the invasive-strategy group at hospital discharge, at 1 month and at 1 year of follow-up[19]. These data, although not conclusive, support a non-invasive approach to risk stratification in those patients in whom an ischemia-guided stratification might succeed in avoiding unnecessary invasive procedures. Again, in this study the very high risk non-Q-wave myocardial infarction patients

with ongoing ischemic complications in the coronary care unit were excluded because of the likelihood that they required coronary revascularization. Nevertheless there is a trend towards the increasing use of coronary angiography and anatomically-guided revascularization for patients recovering after an uncomplicated myocardial infarction, but practice is not synonymous of evidence-based medicine and guidelines cannot be drawn on the basis of habit and routine. The routine use of pharmacological stress echo provides a particularly robust approach for a non-invasive risk stratification policy, selecting for angiography patients already considered eligible to coronary revascularization on the basis of an ischemia-guided approach. Cost-effectiveness studies are needed in order to identify the best algorithm of stratification in post-acute myocardial infarction patients because only a multicenter, randomized, international, prospective trial will offer this essential answer on the basis of evidence rather than of opinion[20].

Conclusions

In patients recovering after an acute uncomplicated myocardial infarction, pharmacological stress echocardiography, through the parameters of timing, severity and extent, provides critical information obviating the need for invasive and more costly cardiac catheterization in most patients. The data on its prognostic power of stratification were obtained through large scale, multicenter, observational trials providing a clinically realistic picture easily reproducible in any echocardiographic laboratory. Pharmacological stress echocardiography can represent a non-invasive filter to refer to coronary angiography only patients with more prognostically malignant forms of coronary artery disease. As written by Maseri[21], "many patients are more amenable to the suggestion of a major intervention (which requires them to be a 'hero' once) than to the suggestion that they change their lifestyle (thus requiring to be a 'saint' forever): a negative dipyridamole stress echo, on the basis of the evidence present in the literature and largely built by the Italian stress echo community, identifies ordinary people, neither hero nor saint".

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