Focus on

Risk stratification of patients after uncomplicated acute myocardial infarction: is there still a need for stress testing?

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Introduction

The goal of risk stratification after acute myocardial infarction is to identify patients whose outcome can be improved through specific medical interventions. Current clinical practice in patients presenting with symptoms of acute myocardial infarction is based on prompt reperfusion (either with angioplasty or thrombolysis) and on early coronary angiography in patients with a complicated course. Patients with an uncomplicated course (no heart failure, no recurrent angina, no electrical instability) generally undergo predischarge exercise electrocardiography which will dictate subsequent management[1]. In the last few years, imaging stress testing with either ultrasound or nuclear techniques has been proposed as a useful method in addition or as an alternative to exercise electrocardiography. This has led to a paradoxical situation wherein a number of more or less sophisticated imaging modalities has been increasingly applied to select the few patients prone to develop cardiac events in a broad population with a very low inherent risk[2].

The aim of this editorial was to elucidate the relative role of clinical variables and predischarge stress testing for risk assessment after acute myocardial infarction. In particular, the role of dobutamine stress echocardiography is discussed in more detail, with a review and comment of the pertinent literature on this topic.

Acute evaluation

Risk stratification must begin when acute myocardial infarction is diagnosed[3]. Patient history and clinical findings may suffice to provide useful information. Patient age, heart failure, anterior infarction, previous infarction, hypotension, tachycardia, diabetes mellitus, smoking, hypertension, female sex, and previous vascular disease have all been defined as important risk factors[4-9], and the presence of these risk factors should always be incorporated in the initial evaluation. Furthermore, the allocation of patients in risk categories is of paramount importance for the selection of subsequent patient management and for interpretation of noninvasive stress test results.

Hospital stay

The main issue related to patient management during hospital stay is the challenge between "aggressive treatment versus early discharge"[10]. Recurrent ischemia, electrical instability, mechanical complications (ventricular septal defect, mitral regurgitation, free wall rupture) or pump dysfunction should be strongly considered for more aggressive interventions including cardiac catheterization. On the other end of the spectrum, patients should be continually assessed for the possibility of early discharge. For patients who have had an uncomplicated course, the final predischarge risk can be assessed about 4 to 5 days after infarction.

Predischarge risk stratification

The extent of left ventricular dysfunction is the most important predictor of postin-

farction mortality. Early studies showed that there was an almost logarithmic inverse relationship between ejection fraction and cardiac mortality, with events increasing sharply in patients with an ejection fraction < 40%[11,12]. This relationship has held true even in the thrombolytic era[13]. Thus, patients with an uncomplicated course but with a left ventricular ejection fraction < 40% should undergo cardiac catheterization.

Among patients with a left ventricular ejection fraction > 40%, clinical judgment has the potential of allocating patients in different risk categories. Three trials prospectively examined clinical and noninvasive laboratory data to predict patients at a low risk of death or reinfarction. In the TIMI II trial, eight factors were identified as prognostic determinants of 6-week mortality[14]. These factors were ranked as follows: rales in ≥ 1/3 of the lung field, age > 70 years, atrial fibrillation, hypotension and sinus tachycardia, diabetes mellitus, previous infarction, female gender, and anterior infarction. The 6-week mortality rate according to the number of these risk factors is reported in figure 1[14]. From this figure the difference between patients with no or with one risk factor (mortality ranging from 1.5 to 2.3%) compared to patients with two or more risk factors (mortality ranging from 13 to 17%) is evident.

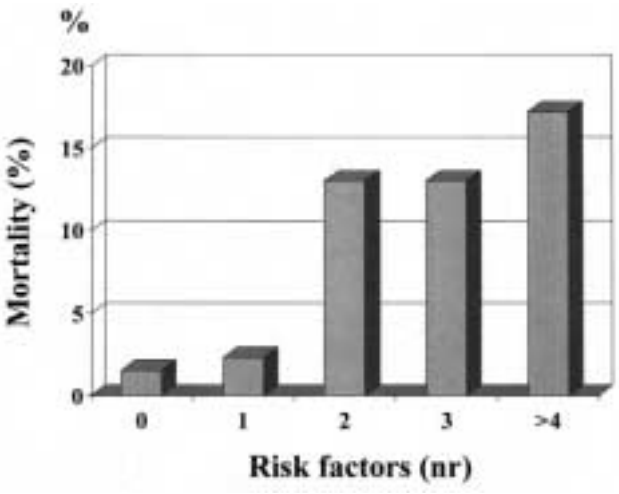

Figure 1. *Mortality at 6 weeks according to the number of risk factors. From the TIMI Study Group[14], modified.*

In the GISSI-2 study, the five most important independent predictors of mortality included ineligibility for the exercise test (relative risk-RR 3.3), left ventricular failure (RR 2.5), echocardiographic left ventricular dysfunction (RR 2.5), electrical instability (RR 1.6), and age > 70 years (RR 1.56)[15]. Interestingly, a positive exercise test was not an important predictor. The independent predictors of nonfatal reinfarction were ineligibility for exercise testing, previous myocardial infarction, and postdischarge angina. Again, a positive exercise test was not predictive of reinfarction.

In the GUSTO I trial, at multivariate analysis the five most important clinical predictors of 30-day mortality were age, systolic blood pressure, Killip class, heart rate, and infarct location[16].

All these studies consistently indicate that, in patients with preserved left ventricular function, the absence of clinical risk factors identifies a subgroup of patients with a very low likelihood of future cardiac events. Such a population of patients has an incidence of adverse irreversible events so low that prophylactic intervention would be unlikely to alter it. By definition, such patients would not require extensive postinfarct testing, as their event rates would naturally be so low as to negate any value of subsequent intervention.

Role of stress testing

Exercise electrocardiography. The main purpose of exercise testing in patients initially treated by acute reperfusion is the assessment of functional status and, possibly, risk stratification for future ischemic events. The issue whether and when to perform the exercise stress test after myocardial infarction remains controversial. Early exercise testing before discharge was the gold standard in the prethrombolytic era when other assessments were often not performed and it is well known that patients who, because of cardiac limitations, are not eligible for stress testing have a high risk of dying during the subsequent year[17]. Few studies have determined whether stress tests add any information to that obtained from the physician's clinical assessment. For instance, in the Multicenter Postinfarction Research Group study, exercise stress testing (as well as Holter monitoring) failed to provide additional prognostic information beyond that obtained from clinical variables and ejection fraction (Fig. 2)[18]. Nowadays, given the relatively low rate of mortality following acute reperfusion, the high ancillary use of coronary angiography and the shortening of hospital stay to < 5 days, standard exercise testing may be of limited use. Most of the large thrombolysis trials have found a low mortality rate (1-2%) 1 year after discharge. The predictive value of early exercise testing is thus low and false positive results are common.

Results from a meta-analysis of studies of exercise electrocardiography showed that the positive predictive value (for cardiac death or myocardial infarction) ranged from 16 to 21%, according to the marker considered (S-T segment depression, impaired systolic blood pressure)[19]. Thus, given the low event rate in the tested population (overall 1-year mortality rate, 3.3%), the positive predictive values are low for all of these tests. Conversely, the negative predictive value of exercise electrocardiography is approximately 90%[3].

Analysis of the GISSI-2 data base also indicates that, for patients with a positive exercise test, the 6-month mortality was 1.7 versus 0.9% for those with a negative

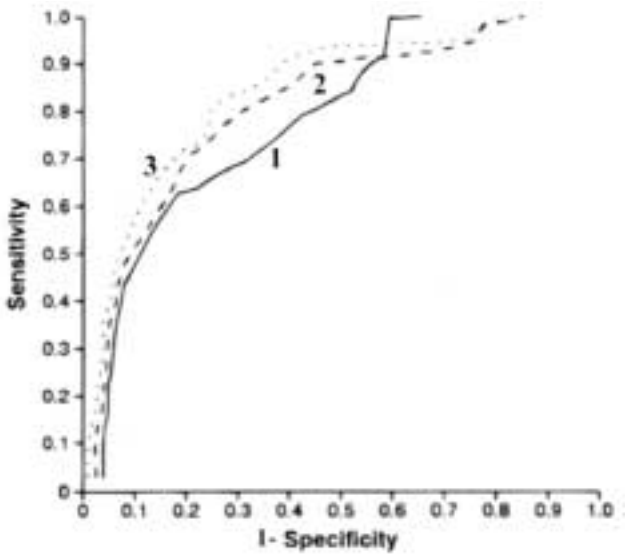

Figure 2. *Incremental prognostic value of diagnostic tests above clinical variables after acute myocardial infarction. Receiver-operator characteristic curves are presented for historical and clinical data (1), radionuclide ventriculography (2) and exercise test variables (3). The improvement in sensitivity and specificity by additional information from the radionuclide scan and exercise test is clinically insignificant. From Tibbits et al.[18], modified.*

test[20]. Thus, although a negative test is reassuring, patients with a positive exercise test still have a > 98% chance of survival over the ensuing 6 months. Although the addition of echocardiographic or nuclear imaging techniques will increase the sensitivity of functional testing, the very low event rates preclude a useful predictive accuracy for such tests, as many false positive results will occur.

Myocardial perfusion imaging. Pooled data from 894 patients, derived from a meta-analysis of studies of exercise perfusion imaging, showed that the presence of a reversible perfusion defect was more sensitive than routine exercise electrocardiography, at the cost of reduced specificity[19]. Positive and negative predictive values were 16 and 95% respectively. Given these findings, one wonders if there is any rationale for the routine use of myocardial perfusion imaging in patients recovering from an uncomplicated acute myocardial infarction.

Stress echocardiography. A large-scale multicenter trial has demonstrated that, early after uncomplicated myocardial infarction, dipyridamole echocardiography is feasible and safe and allows effective risk stratification on the basis of the presence, severity, extent and timing of the induced dyssynergy[21]. However, just as for exercise electrocardiography, the positive predictive value of dipyridamole echocardiography was low, rendering the practical management of patients with a positive response still uncertain. In contrast, the test had an excellent high negative predictive value and this constituted the background for an early discharge strategy[22]. Studies of algorithms of patient selection for testing are needed to compare the relative information gain, risk and cost[23]. Finally, comparative studies in the same patient groups indicate that echocardiographic imaging during dipyridamole infusion is superior to scintigraphy for predicting events after uncomplicated acute myocardial infarction[24,25].

Dobutamine stress echocardiography has recently been applied for evaluating the risk of subsequent cardiac events after acute myocardial infarction. Studies including > 100 patients and addressing this issue are reported in table I[26-31]. All these studies include patients with an uncomplicated course, the vast majority with a first myocardial infarction, in whom a globally good outcome can be anticipated. A maximum dose of 40 mcg/kg/min, plus atropine if needed, was used in all the studies. With the exception of one[28], all studies evaluated both myocardial viability and residual myocardial ischemia. However, there is significant heterogeneity in the diagnostic criteria for defining the presence of myocardial viability. These were based on the improvement in the contractility of a different number of myocardial segments (1 or 2 or 3). Alternatively, a decrease > 0.22 in the infarct zone wall motion for the diagnosis of myocardial viability was considered[31]. As a consequence, even the criteria for diagnosis of myocardial ischemia were slightly different. Cardiac events considered at follow-up were cardiac death, nonfatal myocardial infarction, and unstable angina. Sustained ventricular tachycardia, ventricular fibrillation, and congestive heart failure requiring hospitalization (which was responsible for about one fourth of the events) were also included in one study[26]. In all these studies, positivity of the test was based on the evidence of myocardial ischemia, including new wall motion abnormalities, worsening of resting dyssynergies, or a biphasic response. The prognostic value of dobutamine echocardiography observed in the different studies according to this definition is reported in table I. In most of the studies, negative predictive values ranged from 88 to 90% for all events, 95-98% for hard events, and 98-99% for death[27,28,31]. Positive predictive values ranged from 10 to 23% for all events, 5-11% for hard events, and 2-4% for cardiac death. Two other studies showed higher positive and lower negative predictive values[29,30]. This finding reflects the high number of positive tests observed in these series of patients (63 and 62%, respectively) and can be primarily related to the population studied (all thrombolysed patients in one study[29]; high percentage – 58% – of non-Q wave myocardial infarction in the other study[30]). Nevertheless, despite the different criteria adopted for defining myocardial ischemia and the different events considered at follow-up, the role of dobutamine-induced myocardial ischemia as a risk factor after uncomplicated acute myocardial infarction is consistent in all the studies reported in the literature. Moreover, the only head-to-head comparative predischarge study between dobutamine and dipyridamole stress echocardiography in patients with acute myocardial infarction showed a similar prognostic value for the two types of stress[32].

Table I. Studies addressing the prognostic value of dobutamine-atropine stress echocardiography after uncomplicated acute myocardial infarction.

Author	Patients (n =)	Male (n =)	Age (years)	Q wave (n =)	TL (n =)	Day	Viability (criteria)	Ischemia (criteria)	Events (n =)	Follow-up (months)	PPV (all)	NPV (all)	PPV (hard)	NPV (hard)	PPV (death)	NPV (death)
Carlos et al.[26]	214	163	58 ± 13	NA	121 (57%)	2 ± 7	≥ 3 segments	New WMA, worsening, or biphasic in ≥ 2 segments	CD, MI, UA sustained VT/VF, CHF req hosp (15, 15, 31, 5, 14)	> 12	–	–	–	–	–	–
Sicari et al.[27]	778	677	58 ± 10 (< 75)	572 (73%)	450 (58%)	12 ± 5	Improvement ≥ 1 grade in ≥ 1 segment	New WMA, worsening, or biphasic (n = 436; 56%)	CD, MI, UA (14, 24, 63)	9 ± 7 (1-59)	14%	88%	5%	95%	2.2%	98.9%
Bigi et al.[28]	406	353	57 ± 9 (< 75)	355 (87%)	220 (54%)	10 ± 4	Not evaluated	New WMA, or worsening (n = 192; 47%)	CD, MI, UA	8.8 (1-25)	10%	90%	–	–	–	–
Previtali et al.[29]	152	142	54 ± 8 (< 70)	112 (74%)	152 (100%)	9 ± 5	Improvement in ≥ 2 segments (or ≥ 1 segment if only 2 were asynergic)	New WMA, worsening, or biphasic (n = 95; 62%)	CD, MI, UA (4, 6, 53)	15 ± 19	54%	79%	10%	100%	4.2%	100%
Wang et al.[30]	273	206	NA	168 (62%)	NA	14 ± 8	NA	New WMA, worsening, or biphasic (n = 171; 63%)	Death, MI, UA (18, 18, 54)	14 ± 8 (1-29)	43%	83%	15%	90%	6%	93%
Salustri et al.[31]	245	210	60 ± 10	217 (89%)	118 (48%)	6 to 14	IZ-WMSI decrease > 0.22	WMSI increase > 0.22 (n = 115; 47%)	CD, MI, UA (7, 9, 24)	17 ± 13 (1-44)	23%	89%	11%	98%	4%	98.5%

all = all events; CD = cardiac death; CHF = congestive heart failure; hard = hard events; IZ = infarct zone; MI = myocardial infarction; NA = not available; NPV = negative predictive value; PPV = positive predictive value; req hosp = requiring hospitalization; TL = thrombolysis; UA = unstable angina; VT/VF = ventricular tachycardia/ventricular fibrillation; WMA = wall motion abnormalities; WMSI = wall motion score index.

The prognostic value of viable myocardium after acute myocardial infarction has been questioned. For instance, viable myocardium has been associated with the occurrence of unstable angina at follow-up[27], but also lack of viability has been associated with an adverse outcome[26]. In contrast, in two studies, myocardial viability did not show an independent prognostic value[29,31]. When interpreting these controversial findings, the different echocardiographic criteria of myocardial viability and the clinical endpoints adopted in the different studies should be kept in mind (Table I). Moreover, sustained improvement in the infarct zone throughout dobutamine infusion occurs in a minority of patients, often being followed by deterioration at high doses (biphasic response). In this circumstance the unfavorable prognostic weight is carried by the ischemic phase, rather than by the viability. Thus, one can conclude that, after uncomplicated acute myocardial infarction, the presence of contractile reserve *per se*, at a low dose of dobutamine, is not associated with a worse outcome, unless further deterioration in wall motion occurs at higher doses. Lastly, it should be pointed out that, in general, the identification of viable myocardium in patients with a preserved left ventricular ejection fraction is of little clinical relevance, while, in patients with global left ventricular dysfunction, the assessment of both contractile reserve and myocardial ischemia may identify different subgroups of patients and potentially unmask substantial prognostic heterogeneity[33]. The practical implications of this functional approach in patients with left ventricular dysfunction (may patients with a pronounced viability response at low-dose dobutamine and without inducible ischemia at high doses avoid cardiac catheterization and be left on medical therapy? should we revascularize all patients with a significant contractile reserve?) are still unclear.

In summary, similar to exercise electrocardiography, dobutamine echocardiography has a high negative predictive value, and is able to discriminate the subgroup of patients with a higher likelihood of an adverse outcome[34]. What is, then, the practical prognostic benefit of predischarge dobutamine echocardiography in these patients? Again, we believe that the indication for this stress test should be tailored according to the clinical scenario. Risk stratification by clinical variables allows to discriminate patients with a different outcome. In patients with an intermediate risk at clinical judgment (age > 60 years or diabetes mellitus) the response to the dobutamine stress test can be used to distinguish patients according to the risk of future cardiac events[31].

Conclusions

The questions now are: which of the noninvasive tests is the most predictive and cost-effective, and do we need them for every patient? The time of disregarding all the information derivable from stress testing has not yet come. Rather, the aim of this editorial was to re-emphasize the concept that, after an uncomplicated acute myocardial infarction, indications for stress testing should be accurately tailored on individual basis and the prognostic information should be put in the larger context provided by the clinical picture.

We do not have a definite answer yet. However, from the studies available in the literature and our own experience, the following conclusions can be drawn. In the reperfusion era, the left ventricular ejection fraction still plays a major role in the prognostic assessment of patients with an uncomplicated course. Thus, patients with a left ventricular ejection fraction < 40% should undergo coronary angiography. Patients with a left ventricular ejection fraction > 40% usually undergo a predischarge stress test, with a preference for exercise electrocardiography because of practical reasons. However, in this population, the appropriate application of Bayesian analysis demonstrates that the large number of false positive test responses (independent of the test employed) is a consequence of the extremely low pretest likelihood of disease and often leads to further noninvasive and invasive testing at substantial cost and some risk to these patients. Thus, risk stratification, on the basis of clinical variables alone, should form the basis for subsequent noninvasive stress testing strategies. Patients with a clinical risk factor ≤ 1 will probably have no additional information from the results of any stress testing. On the other hand, it is likely that the presence of several risk factors has a negative prognostic impact, beyond the results of stress tests. The efficacy of this assumption should be verified in prospective large-scale clinical studies.

We are entering a new era where prognostication of patients after uncomplicated acute myocardial infarction will be debated. Until conclusive results are available, we should avoid confusion and remember that "the multiplicity of prognostic indicators identified poses practical difficulties for physicians who have no established institutional policy to follow. On the one hand, they may have difficulty in choosing a single test; on the other, when they choose to apply multiple tests, they may have difficulty in interpreting the conflicting results. They should not be tempted to disregard all the clues available from the clinical follow-up and from routine tests in favor of a single test that was shown to be highly predictive in a report published in a major journal, unless it is clear in which specific subgroup of patients and under what conditions it has the prognostic value reported"[35].

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