Usefulness of exercise test in selected patients coming to the emergency department for acute chest pain

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Chest pain;
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Background. **The management of patients with acute chest pain is a common and difficult challenge for clinicians. In our emergency department (ED) a systematic protocol that involves the use of the exercise test for the management of patients with chest pain of suspected cardiac origin is presently running. The aim of the present study was to evaluate the feasibility of such a test in this setting, in terms of the safety and satisfactory follow-up of these patients discharged home.**

Methods. **Patients with chest pain lasting ≤ 24 hours, aged > 18 years, without a history of trauma or of any other evident medical cause of chest pain and without high-risk characteristics were included in the present study. These patients, defined as low-risk patients for acute coronary events on admission, were evaluated in the ED area and submitted to serial ECG and blood sampling for the determination of the creatine kinase-MB mass and troponin I serum levels on admission and at 6 and 12 hours after admission. A symptom-limited maximal exercise was performed in the patients with a negative clinical observation and typical chest pain or atypical chest pain but multiple coronary risk factors.**

Results. **In the year 2000, 1370 patients were evaluated in the ED for chest pain. In 150 (11%) an exercise test was performed. The test was positive in 24 patients (16%). The criteria for a positive test were only clinical in 3 patients, only ECG in 13 patients, and both in 8 patients. Inconclusive tests were observed in 27 patients (18%) and the test was negative in 99 patients (66%). There were no complications during the exercise test. At a median follow-up of 237 days (range 11-443 days), 11 clinical events were recorded (4 acute coronary syndromes and 7 revascularization procedures). Patients with a non-negative exercise test had a significantly shorter event-free survival ($p < 0.005$).**

Conclusions. **The exercise test performed in selected patients coming to the ED with acute chest pain is safe and useful for further risk assessment.**

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Introduction

Chest pain is by far the leading cause of urgent admission to the emergency department (ED) in western countries. Its proper triage and consequent treatment are crucial to avoid inappropriate discharge in the presence of life-threatening disease on the one hand and unnecessary hospitalization when major diseases are absent on the other[1-6].

We recently developed and validated a systematic approach to all patients coming to the ED for chest pain[7] (Fig. 1). The possible value of the exercise test as a part of a pre-specified and systematically applied protocol of chest pain triage has not yet been extensively investigated in the setting of real clinical practice.

Therefore, the aim of the present study was to assess the safety, feasibility and usefulness of the exercise test in consecutive patients coming to the ED for chest pain, selected on the basis of a specific protocol applied in routine clinical care at our Institution.

Methods

In our hospital a "chest pain project" was started in 1999, in order to improve the management of patients with acute chest pain admitted to the ED. To minimize inappropriate discharge and hospital admission, a consensus protocol was adopted and prospectively tested after several meetings with all the staff physicians of the Cardiology Unit and with the ED staff, with the clinical and technical support of the Clinical Laboratory. This protocol has been previously approved and validated in a prospective follow-up study[7].

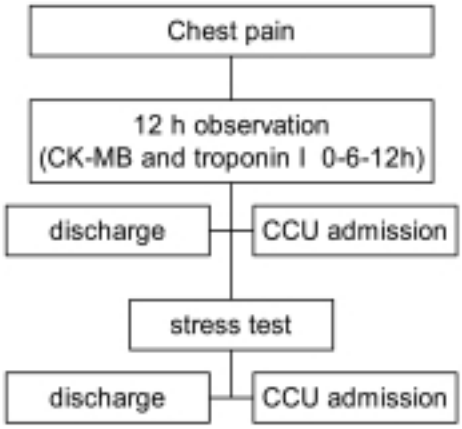

Figure 1. *Proposed algorithm for the management of patients with acute chest pain. Patients with chest pain were evaluated in the Emergency Department area by means of serial ECG and sampling of the creatine kinase (CK)-MB mass and troponin I serum levels at the time of admission and at 6 hours and 12 hours after admission. A treadmill stress test was performed in selected cases. CCU = coronary care unit.*

In the present study the inclusion criteria were: age > 18 years, chest pain lasting ≤ 24 hours, informed consent to subsequent follow-up. The exclusion criteria were: a history of trauma or of any other evident medical cause of chest pain and high-risk factors. Table I shows the identification criteria for high-risk patients.

The data were collected by physicians at the time of arrival of the patients and reported on a specific form which included: the time of onset, duration and characteristics of the chest pain, the family history, major risk factors for coronary heart disease, the presence of a previous history, if any, of cardiac-related diseases, a previous history of coronary revascularization, physical examination and ECG findings.

Chest pain characteristics. Typical angina was defined as a deep, poorly localized chest discomfort (or discomfort of the jaw, neck, ear, arm and/or epigastrium) that was reproducibly associated with physical exertion or emotional stress and promptly relieved by rest and/or sublingual nitroglycerin. Angina was defined as unstable if the episodes were more severe and prolonged or if they occurred at rest, or were precipitated by less exertion than previously. Features that were not characteristic of typical angina were considered as atypical chest pain.

Table I. Definition of "high-risk" patients.

Typical chest pain lasting > 20 min
ECG evidence of myocardial ischemia
Ongoing typical chest pain
Typical chest pain lasting < 20 min in the presence of:
- known coronary artery disease
- diabetes mellitus
- at least two coronary disease risk factors
Congestive heart failure at the initial clinical examination
Other potential life-threatening conditions at the initial clinical examination

Electrocardiographic findings. ST-segment changes were considered ischemic if ≥ 0.05 mV in one or more leads. Inverted T waves were considered ischemic if symmetric and ≥ 0.2 mV in one or more leads[8]. The remaining changes were considered as non-specific.

Patients included into the study were evaluated by blood sampling for the determination of the creatine kinase (CK)-MB mass and of the troponin I serum levels on admission and 6 and 12 hours later. During this time the patients remained in the ED. A 12-lead ECG was also obtained at 6 and 12 hours after admission (Fig. 1). Additional ECGs were obtained for episodes of chest pain or of suspected ischemia. The ECGs were interpreted by the attending cardiologist.

After 12 hours, a consensus was again achieved by integrating the clinical and laboratory data and a decision was made on the basis of the following:
1. patients with a negative clinical course for an acute coronary syndrome (ACS), without biochemical evidence of myocardial damage or an evolving ECG and without recurrent symptoms while under observation, were discharged early and sent home (classified as non-ischemic chest pain) with or without being submitted to the treadmill stress test in accordance with the ANMCO-SIC guidelines[9]. Patients with typical chest pain and patients with atypical chest pain but multiple (> 2) coronary risk factors or diabetes mellitus were submitted to the exercise test, if they were able to perform exercise;
2. patients with a positive clinical course or ECG/biochemical test results suggestive of an ACS were hospitalized.

Laboratory data. CK-MB mass and troponin I assays were determined using the same immunometric method (Dade Behring, Liederbach, Germany). A CK-MB mass ≥ 5 ng/ml and troponin I levels ≥ 0.13 ng/ml were considered positive.

A diagnosis of an acute myocardial infarction was made if symptoms were consistent with myocardial ischemia with a characteristic time-related increase in CK-MB mass (a CK-MB value greater than the upper limit of the reference range).

Exercise test. The exercise test was performed by staff cardiologists (the treadmill test was available between 8.00 a.m. and 3.00 p.m., 5 days a week) usually within 12 hours after the end of the observational period (no more than 72 hours). A symptom-limited exercise test was usually performed by means of a treadmill test with the Bruce protocol with a continuous 12-lead ECG and non-invasive blood pressure monitoring. When specifically requested by the patient (because of a partial inability to walk and run), a bicycle ergometer test was applied, starting with 20 W and increasing the workload by 20 W every minute. The applied criteria for a positive

exercise test were those recommended by the American College of Cardiology/American Heart Association guidelines for exercise testing[10]. The test was considered diagnostic when the peak heart rate was ≥ 85% of the age-predicted maximum or when the maximum workload completed was 6 METS (4 METS for patients aged > 75 years). The test was considered doubtful when symptoms or the ECG changes were not clearly interpretable. When pooled together, positive, non-diagnostic and doubtful tests were defined as non-negative tests.

Follow-up. Clinical follow-up was obtained by either outpatient clinical visits or telephone interviews made by members of the medical staff. A pre-defined list of significant clinical events was established and recorded in a hierarchical order: any cause of death, hospital admission for documented ACS and procedures of myocardial revascularization. If patients had more than one event, only the most relevant was considered.

Statistical analysis. Data are presented as mean ± SD. For group comparisons between patients with negative and non-negative test results, the χ^2 and unpaired Student's t-tests were used. Multivariate analysis was performed by using a linear regression model with a stepwise method. The variables considered in the model were preplanned or selected on the basis of the best univariate tests. Survival analysis was performed by the use of the Kaplan-Meier tables with the log rank test for differences between groups. A SAS statistical software for PC was used (SAS Institute, Cary, NC, USA).

Results

Between January 1 and December 31, 2000, 1370 patients were examined in the ED for chest pain. One hundred and fifty patients (11%) were selected on the basis of the afore-mentioned criteria. This group constituted 9% of the total standard exercise tests performed in our department. The clinical characteristics of the study group are given in table II. A positive exercise test was observed in 24 patients (16%). The criteria for a positive exercise test were only clinical in 3 patients (11%), only ECG in 13 patients (55%), and both in 8 patients (33%). Inconclusive or non-diagnostic tests were observed in 27 patients (18%) and the test was negative in 99 patients (66%). No adverse effects attributable to the exercise test were observed. Table III shows the characteristics of the patients divided according to the results of the exercise test.

Table II. Characteristics of the patients undergoing the exercise test.

No. patients	150 (9% of the total exercise tests of 2000)
Age (years)	61 ± 11
Males	63%
Risk factors	
Family history	28%
Cigarette smoking	15%
Diabetes	11%
Hypertension	47%
Hypercholesterolemia	37%
Typical chest pain	37%

Among the 24 patients with a non-negative test, 19 (79%) underwent coronary angiography and/or stress myocardial scintigraphy. In 53% of the patients with a positive test there was a documented scintigraphic defect or a critical coronary stenosis. In all patients with a non-negative test anti-ischemic pharmacological therapy was started or potentiated.

Follow-up data were available for 129 patients (86%). The median follow-up was 237 days, ranging from 11 to 443 days.

Eleven clinical events were recorded: 4 cases of hospital admissions for ACS and 7 cases of myocardial revascularization procedures (3 coronary angioplasty and 4 coronary artery bypass graft). The details of the 11 patients with significant clinical events at follow-up are shown in table IV: there were 2 admissions for ACS in the group of patients with a negative test, and 2 admissions for ACS and 7 revascularization procedures in the group of patients with a non-negative test.

Analysis of the survival curves revealed a highly significant and better event-free survival in patients with a negative exercise test compared to patients with a non-negative test (Fig. 2).

Discussion

The safe and cost-effective management of patients presenting to the ED because of chest pain continues to

Table III. Patient characteristics according to the exercise test results.

	Negative	Inconclusive	Positive	p
No. patients	99	27	24	
Age (years)	59 ± 11	64 ± 11*	62 ± 10	< 0.05
Males	68%	44%	67%	0.08
Previous known CAD	15%	37%*	54%*	< 0.0001

CAD = coronary artery disease. * vs negative. Predictive value of test results (multivariate analysis): previous known CAD only.

Table IV. Details of patients with clinical events at follow-up.

Patient	Sex	Age (years)	Typical chest pain	Exercise test results				Event
				Clinical	ECG	Max HR (%)	Max workload (METS)	
1	M	49	Yes	-	-	81	12	ACS
2	F	79	No	-	-	87	6	ACS
3	M	60	Yes	-	?	71	9	ACS
4	F	72	No	?	-	105	4	ACS
5	F	72	Yes	-	+	93	10	CABG
6	F	68	No	+	+	56	7	CABG
7	F	60	No	+	+	71	10	CABG
8	M	77	No	+	?	75	6	CABG
9	M	51	Yes	+	+	83	7	PTCA
10	M	69	Yes	+	+	68	5	PTCA
11	F	69	No	+	+	70	4	PTCA

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; HR = heart rate; PTCA = percutaneous transluminal coronary angioplasty.

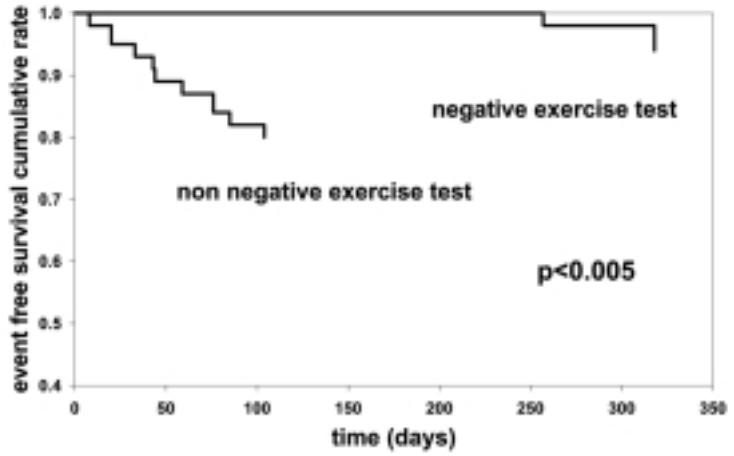

Figure 2. *Analysis of the survival curves of patients with a negative exercise test compared to patients with a non-negative exercise test.*

be a major clinical challenge. Current strategies entail accelerated diagnostic protocols comprising 6 to 12 hours of observation and the measurement of cardiac injury markers, which, if negative, may be followed by exercise ECG testing before or shortly after discharge[11-18].

Despite the presence of serial published data on the role of the exercise test in patients coming to the ED with chest pain, its use in a specific setting of a standardized protocol for chest pain triage has not yet been clearly established in routine clinical practice[1,4-6,12-25]. Some studies were retrospective, or did not specify the selection criteria, or the patients were all the same admitted to the hospital, or were rather selected on the basis of a subjective clinical evaluation[15,17,19-21]. On the other hand, some institutions, despite the presence of a specific protocol for the assessment of patients referred for chest pain, do not include an exercise test in their flow chart or else the criteria for performing such a test are not clearly established[24].

The largest reported study of exercise ECG testing as part of a chest pain protocol included 1010 patients[19]. This study supports the safety of symptom-limited exercise ECG testing for patients with a low prevalence of disease and reports a high negative predictive value for 30-day cardiac events. Unfortunately, this was a retrospective analysis.

The Rapid Rule Out of Myocardial Ischemia Observation (ROMIO) study prospectively evaluated 100 patients with chest pain who were randomly assigned to regular care (admission) or to an ED-based rapid rule-out protocol that included serial CK and CK-MB levels (0, 3, 6 and 9 hours), serial ECG and, if results were negative, a predischarge exercise test[20]. There were no adverse effects during exercise testing and the length of stay and total costs were significantly lower in the chest pain center protocol group. Despite the fact that the study period was 19 months, only 50 patients were selected for the chest pain protocol; therefore this study was characterized by a very accurate pre-selection of the patients.

Zalenski et al.[17] documented the incremental diagnostic value, as analyzed using the receiver-operating curve, of exercise ECG testing when associated with serial CK-MB and serial ECG testing. In their series, however, all patients remained hospitalized. In their work Polanczyk et al.[15] presented the in-hospital and 6-month outcome of 276 chest pain patients determined, using the Goldman algorithm, to be at low risk. Patients underwent symptom-limited exercise tests within 48 hours of their presentation with chest pain. There were no adverse events related to the exercise ECG test and the 6-month events rate in patients with a negative test was 2% (negative predictive value 98%) in contrast to an event rate of 15% in patients with positive or equivocal tests. They concluded that exercise ECG testing can be safely used to identify patients at low risk of subsequent events and that patients without a clearly negative test are at an increased risk for readmission and cardiac events. Even in this paper, however, after the observational period the patients were not sent home and they were all hospitalized.

Another study applied a follow-up design to determine the prognostic effect of graded exercise ECG testing in patients with low- to moderate-risk chest pain evaluated in an ED 9-hour protocol chest pain center[21]. A series of 958 patients was studied and the patients with a positive, inconclusive, and normal stress test had complication rates of 36.8, 3.4 and 1.1% respectively. A high percentage of tests was found to be inconclusive (34%). These latter patients also had an increased risk for future cardiac events, although this was significantly less than that for patients with a positive stress test. Besides, even this was a retrospective study.

A randomized, controlled trial of 424 unstable angina patients at intermediate risk for short-term cardiovascular events compared the safety, effectiveness, and costs of those admitted to a chest pain center versus those admitted to the hospital[24]. After 6 hours of observation, patients without clinical changes, ECG changes, or CK-MB elevations were submitted to an exercise ECG test. There were no clinical events associated with stress testing. Patients with negative tests were discharged home while patients with equivocal or positive results were hospitalized. Unfortunately, the criteria for performing an exercise test at the end of the observational period were not clearly specified in the paper.

A rather different approach is the one proposed by deFilippi et al.[25], who compared a strategy of predischarge coronary angiography to exercise testing in low-risk patients, in order to reduce repeat ED visits and to identify additional coronary artery disease. Coronary angiography revealed disease (≥ 50% stenosis) in 19% and exercise ECG testing was positive in 7% of the patients. During follow-up, patients with a negative angiography had fewer returns to the ED and hospital admissions, compared with patients with a negative exercise test. This study may suggest that a more aggressive diagnostic tool offered by the coronary angiogram may lead to a better risk stratification of the patients. On the other hand such an approach has some obvious limitations in terms of ethical and logistic considerations. Moreover, a cost-benefit analysis should be performed by comparing such an approach to the rapid rule-out protocol applied in the chest pain centers.

Table V[15,17,19-21,24] summarizes the main results of these studies.

Table V. Summary of the studies using exercise test in chest pain protocols.

Author	No. subjects*	Time to exercise test (hours)	Exercise test	Results	Follow-up period	Adverse events during the test
Polanczyk et al.[15]	276	48	Bruce (standard or modified)	P or ND = 81/276 N = 195/276	6 months	0
Zalenski et al.[17]	317 (224)	12	Bruce (standard or modified)	P = 17/224 ND = 59/224 N = 148/224	In-hospital	0
Gibler et al.[19]	1010 (791)	9	Bruce symptom-limited	P = 9/791 ND or N = 782/791	30 days	0
Gomez et al.[20]	50 (44)	9	Cornell symptom-limited	P = 2/44 ND = 1/44 N = 41/44	30 days	0
Diercks et al.[21]	1209 (958)	9	Bruce symptom-limited	P = 27/958 ND = 326/958 N = 27/958	1 year	0
Farkouh et al.[24]	424 (152)	6	Not specified	P or ND = 55/152 N = 97/152	6 months	0

N = negative test; ND = non-diagnostic test; P = positive test. * total number in the study (patients who underwent exercise test).

At our institution a systematic approach to all patients coming to the ED for chest pain is presently running. This approach has been recently validated by a 1-year follow-up[7]. The purpose of the present paper was to evaluate, in terms of its safety, feasibility and usefulness, the exercise test performed in a group of patients selected from the overall population presenting to the ED with chest pain. The selection we applied was based on a stratification obtained at two different levels: first in the ED environment and then in the cardiology department. At the ED level patients with a very low likelihood of coronary artery disease according to the analysis of the coronary risk profile and chest pain characteristics were immediately sent home with no other cardiac examination or they were submitted to other specific examinations. Patients in whom the diagnosis was still uncertain underwent a 12-hour observational protocol. After this period a cardiologist applied a further stratification algorithm, according to the results of the observation, classifying the patients as being either eligible for discharge or for an exercise stress test. Applying this strategy, the patients who were ultimately submitted to the exercise test were 11% of the initial population of patients with chest pain and accounted for approximately 9% of the standard laboratory procedures.

Despite encouraging data on the safety of the very early exercise test in patients coming to the ED with chest pain[22,23], we preferred to extend the observational period to 12 hours, since we believe that such an approach constitutes a reasonable compromise between the need of a short in-hospital stay and the possibility that the patient goes through life-threatening side effects of the exercise test.

In this setting, according to what observed by other investigators who applied similar protocols[15,20], the exercise test was safe, as none of the 150 patients had adverse effects attributable to the procedure.

Finally, the exercise test performed at the end of the observational period allowed for a further identification of those patients at risk of developing significant clinical events, whereas patients with a negative exercise test could be sent home with a long period of event-free survival.

Among the 99 patients sent home after a negative exercise test, we did not observe any significant clinical event at 1 year of follow-up, with the exception of 2 cases of hospital admissions for documented ACS occurring 8-12 months after the first episode of chest pain. It is interesting to note that these two patients, despite a negative 12-hour observation and a negative exercise test at the time of the first evaluation, had multiple coronary risk factors. This may suggest that the documented ACS observed 8-12 months after the first observation may not be related to the first episode of chest pain but rather to the progression of their coronary artery disease.

Study limitations. First of all, it was performed at a single center with a relatively small number of patients studied. Secondly, most of the clinical events we encountered were myocardial revascularization procedures. This is certainly a surrogate endpoint and it might be artificially increased in those patients with a non-negative exercise test by a more extensive use of coronary angiography.

On the other hand, this simplification had to be applied, similarly to what done by others, because the general population of patients coming to the ED for chest pain has to be considered as being at a relatively low risk and therefore a significant number of hard events cannot be observed by a single center in a reasonable time interval. Moreover, follow-up data were not available for all patients. Due to the small number of cardiac events, this factor could have jeopardized our estimation of the event rate.

Finally, the exercise test was applied to a relatively low-risk population and therefore there was a relatively high number of negative results (66%).

In conclusion, exercise ECG testing performed in selected patients coming to the ED with acute chest pain is safe (no complications reported) and useful for further risk stratification. When the described criteria are applied, the increase in the workload of the Ergometer Laboratory is reasonable. The present study could not address, nor had been planned for, the possible role of plaque instability in the genesis of chest pain in patients presenting to the ED: the value of the additional information provided by the use of the new biochemical indicators of plaque instability in this clinical setting deserves further investigations.

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