Exercise stress testing before and after successful multivessel percutaneous transluminal coronary angioplasty

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Abstract

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Controversy exists regarding the diagnostic accuracy, optimal technique, and timing of exercise testing after percutaneous coronary intervention. The objectives of the present study were to analyze variables and the power of exercise testing to predict restenosis or a new lesion, 6 months after the procedure. Eight-four coronary multi-artery diseased patients with preserved ventricular function were studied (66 males, mean age of all patients: 59 ± 10 years). All underwent coronary angiography and exercise testing with the Bruce protocol, before and 6 months after percutaneous coronary intervention. The following parameters were measured: heart rate, blood pressure, rate-pressure product (heart rate x systolic blood pressure), presence of angina, maximal ST-segment depression, and exercise duration. On average, 2.33 lesions/patient were treated and restenosis or progression of disease occurred in 46 (55%) patients. Significant increases in systolic blood pressure (P = 0.022), rate-pressure product (P = 0.045) and exercise duration (P = 0.003) were detected after the procedure. Twenty-seven (32%) patients presented angina during the exercise test before the procedure and 16 (19%) after the procedure. The exercise test for the detection of restenosis or new lesion presented 61% sensitivity, 63% specificity, 62% accuracy, and 67 and 57% positive and negative predictive values, respectively. In patients without restenosis, the exercise duration after percutaneous coronary intervention was significantly longer (460 ± 154 *vs* 381 ± 145 s, P = 0.008). Only the exercise duration permitted us to identify patients with and without restenosis or a new lesion.

Introduction

The American College of Cardiology/American Heart Association guidelines for exercise testing suggest that functional testing should not be performed routinely in all patients after percutaneous coronary intervention (PCI) (1). Despite technological advances and a better understanding of its pathophysiology, restenosis remains the major limitation of PCI, normally occurring within the first 6 months after angioplasty. A major clinical problem is the noninvasive detection of restenosis among asymptomatic patients,

because silent ischemia has been reported to be a predictor of mortality and cardiac events in patients with coronary artery disease (2-5). Coronary angiography (CA) has been traditionally used as the gold standard for detecting restenosis. However, the cost and invasive nature of angiography have prompted the search for a simpler noninvasive test that could reliably detect restenosis. The standard exercise treadmill test (ETT) is safe, simple, and the most readily available of these tests. Unfortunately, previous studies on the value of ETT for detecting restenosis have yielded conflicting results (6-8).

Thus, the purpose of the present study was to compare ETT before and after PCI and determine the diagnostic value of ETT for detecting restenosis in patients with multivessel coronary artery disease.

Material and Methods

Study population

The study group consisted of 84 patients with multivessel disease who underwent elective PCI as part of the medical, angioplasty and surgical study (9). Selection criteria were: stable angina pectoris, ejection fraction >40% on echocardiography, and at least two critical stenoses (internal diameter reduction >70% by visual assessment) in the proximal two-thirds of two major epicardial coronary artery. Only patients not treated with digoxin, who were in sinus rhythm and without bundle branch block, nonspecific intraventricular block patterns, or any other electrocardiographic abnormalities precluding an accurate resting of the ST segment during ETT were included. Nitrate preparations other than sublingual nitroglycerin and calcium entry blocking agents were withdrawn 4 days before the study, and ß-blocking agents 5 days before, unless withdrawal was considered to be contraindicated by the patient's physician. All patients underwent CA and ETT before and 6 month after PCI. The study protocol was approved by our institutional Ethics Committee and written informed consent was obtained from all patients. Table 1 summarizes the clinical data of the patients.

Coronary angiography and percutaneous coronary intervention

CA and PCI were performed according to standard techniques. All patients underwent CA before and 6 months after PCI. Selective left and right coronary arteriographies and ventriculographies were performed according to the techniques of Sones Jr. and Shirey (10) and Seldinger (11). All CA were reviewed independently of the clinical data by 2 investigators who were blind to the results of the physiological tests. Coronary arteries were submitted to revascularization only in the event of an initial narrowing of ≥70%. A successful PCI was defined as dilation of the stenosis, resulting in a final narrowing of <50%. Patients were considered to have undergone incomplete revascularization if they had stenosis of ≥50% in any coronary artery not submitted to revascularization. Stent implantation and multivessel PCI were performed in all patients. At follow-up, restenosis was defined as a ≥50% luminal diameter stenosis and progress of coronary artery disease when new stenosis was observed in the CA after PCI. The angiographic data are summarized in Table 1.

Exercise test

Symptom-limited ETT (Fukuda Denshii Co. Ltd., Model ML 8000 stress test system, Tokyo, Japan) was performed with 12-lead electrocardiograms during an ETT, using the Bruce protocol, performed before and about 6 months after PCI. The ST segment was measured 0.08 s after the J point in 3 consecutive QRS complexes with a flat base-

line and R wave of equal amplitude. A horizontal depression of ≥0.1 mV for men and of ≥0.2 mV for women occurring with or without chest pain was considered to be a positive electrocardiographic result. End points for terminating exercise were severe angina, dyspnea, extreme fatigue, ST-segment depression of ≥0.3 mV, maximal aged-related heart rate, and the occurrence of other harmful conditions such as hypotension, severe arrhythmia, and dyspnea. Electrocardiographic recordings of all tests were evaluated independently in a blind fashion by two cardiologists; in case of disagreement, the matter was resolved by consensus.

The following parameters were measured: heart rate, blood pressure (systolic and diastolic), rate-pressure product (heart rate x systolic blood pressure), presence of angina, maximal ST-segment depression, and exercise duration in seconds.

Statistical analysis

Categorical values are reported as frequencies and continuous variables as means ± SD. The paired Student *t*-test or unpaired Wilcoxon test was used to compare quantitative variables before and after PCI. Univariate profile analyses were performed to determine the presence of restenosis or of a new stenosis by the ETT. Results of the ETTs were compared with CA data, and calculations of sensitivity, specificity positive and negative predictive values, and diagnostic accuracy were performed. For these last variables, patients who did not achieve an 85% age predictive heart rate were not considered. A P value <0.05 was considered to be statistically significant.

Results

Clinical and coronary angiography data

The baseline clinical and angiographic characteristics of the study are listed in Table

1. A total of 84 patients (66 men) with an average age of 59 ± 10 years were studied. Fifty-six patients (67%) had Q-wave infarct-related vessel PCI in 56 culprit vessels (≥1 month myocardial infarction). Double vessel disease occurred in 42 patients (50%) and triple vessel disease in another 50%. Stent implantation and multivessel PCI were performed in all patients. The diameters of stenosis before and immediately and 6 months after PCI were 84.7 ± 9.6, 15.9 ± 9.6, and 34.8 ± 18.6%, respectively. The numbers of stenoses treated per patient were 2.33 ± 0.87. The treated artery was the left anterior descending one in 68 (41%), the right coronary artery in 55 (33%) and left circumflex artery in 44 (26%) cases. Revascularization was complete (no stenosis >50% in any epicardial coronary artery) in 35 patients (42%). PCI was successful in all of our patients. Angiographic restenosis and new stenosis were detected in 37 patients and 53 vessels (32%) and in 21 patients (25%) and 24 vessels, respectively. Restenosis and/or new stenosis was detected by CA in 46 patients (55%) 6 months after PCI.

Table 1. Clinical and angiographic data of the patients studied.

Clinical data	
Age (years, mean ± SD)	59 ± 10
Men	66 (79%)
Smokers	30 (36%)
Systemic hypertension	63 (70%)
Dyslipidemia	48 (57%)
Diabetes mellitus	36 (43%)
Previous myocardial infarction	56 (67%)
Coronary angiography	
Two vessel disease	42 (50%)
Three vessel disease	42 (50%)
Stenosis before PCI (%, mean ± SD)	84.7 ± 9.6
Stenosis immediately after PCI (%, mean ± SD)	15.9 ± 8.4
Stenosis six months after PCI (%, mean ± SD)	34.8 ± 18.5
Incomplete revascularization	49 (58%)
Follow-up	
Restenosis	37 (44%)
New stenosis	21 (25%)
Restenosis and/or new stenosis	46 (55%)

PCI = percutaneous coronary intervention.

Exercise test

Oral antianginal medication was not stopped before or after PCI in 15 patients because discontinuation was considered to be contraindicated by the patient's physi-

Table 2. Results of the exercise treadmill test before and after percutaneous coronary intervention (P = 0.014; McNemar test).

	After			Total
	Positive	Negative	<85% HR	
Before				
Positive	27 (32%)	12 (14%)	6 (7%)	45 (54%)
Negative	1 (1%)	10 (12%)	9 (11%)	20 (24%)
<85% HR	2 (3%)	8 (10%)	9 (11%)	19 (22%)
Total	30 (36%)	30 (36%)	24 (28%)	84 (100%)

Positive: abnormal electrocardiographic results; negative: normal electrocardiographic results; <85% HR: did not achieve predictive heart rate.

Table 3. Results of the exercise treadmill test (univariate profile analyses).

	All patients (N = 84)	Restenosis and/or new stenosis	
		Yes (N = 46)	No (N = 38)
Heart rate at peak (bpm)			
Before	133 ± 23	133 ± 23	135 ± 23
After	135 ± 18	135 ± 17	135 ± 20
	P = 0.59[#]	P = 0.59[#]	P = 0.79[+]
Systolic blood pressure at peak (mmHg)			
Before	177 ± 28	168 ± 25	188 ± 29
After	186 ± 28	182 ± 28	191 ± 27
	P = 0.02[#]	P = 0.02[#]	P = 0.48[+]
Rate-pressure product at peak (bpm · mmHg · 10^{-3})			
Before	23.8 ± 5.6	22.4 ± 5.1	25.5 ± 5.9
After	25.3 ± 5.4	24.6 ± 5.2	26.0 ± 5.5
	P = 0.04[#]	P = 0.04[#]	P = 0.53[+]
Duration of exercise (s)			
Before	378 ± 155	353 ± 136	407 ± 173
After	417 ± 154	381 ± 145	460 ± 154
	P = 0.00[#]	P = 0.11[#]	P = 0.01[+]
Results of ETT after PCI			
Angina	16	4 (9%)	12 (32%)
Positive	30	20 (44%)	10 (25%)
Negative	30	13 (28%)	17 (45%)
<85% age-predictive heart rate	24	13 (28%)	11 (30%)

ETT = exercise treadmill test; PCI = percutaneous coronary intervention.
[#]P (before *vs* after); [+]P (yes *vs* no).

cian. In these patients, antianginal medication at the time of ETT consisted of ß-blocking agents (N = 21) or calcium-blocking agents (N = 16).

Comparative analysis of the characteristics at peak exercise between the ETT before and after PCI did not show differences in heart rate (133 ± 23 and 135 ± 18 bpm, respectively, P = 0.556), but showed differences in systolic blood pressure at peak exercise (177 ± 28 and 186 ± 28 mmHg, respectively, P = 0.022), rate-pressure product (23.8 ± 5.6 and 25.3 ± 5.4 bpm · mmHg · 10^{-3}, respectively, P = 0.045), and duration of exercise (378 ± 155 and 417 ± 154 s, respectively, P = 0.003). Angina was reported by 27 patients (32%) before PCI and by 16 (19%) after PCI. The magnitude of ST-segment depression tended to decrease after PCI, but with no statistically significant difference (-0.07 ± 0.1 before and -0.05 ± 0.09 mV after PCI, P = 0.09).

Regarding the results of ETT, 45 (54%) and 30 (36%) patients were positive, 20 (24%) and 30 (36%) were negative, and 19 (22%) and 24 (28%) did not achieve 85% of age-predictive heart rate before and after PCI, respectively (Table 2). The present study shows a significant association between these results (P = 0.01). In the majority of cases (54%) the results of ETT were positive before PCI, while the number of the negative tests increased (24 to 36%) after PCI. The 27 patients with a positive test before and after the procedure showed a later appearance of ST-segment depression (250 and 312 s, respectively, P = 0.01) and a tendency to a decrease in the time of duration (354 and 269 s, respectively, P = 0.09) after PCI.

The main parameters of the ETT before and after PCI in patients with and without restenosis and/or new stenosis are summarized in Table 3. No difference was found in heart rate at peak exercise between the first and second tests. Both systolic blood pressure and rate-pressure product at peak exercise were significantly higher during the

ETT after PCI than before PCI in patients with restenosis and/or new stenosis (P = 0.022 and 0.049, respectively). Similarly, duration of exercise after PCI was significantly longer than before PCI, but only for patients without restenosis and/or new stenosis during follow-up (P = 0.008). Of the 16 patients with angina in the ETT after PCI, nine (56%) had restenosis and/or new lesions in the coronary artery.

After PCI, the ETT was positive in 20 patients with restenosis and/or new stenosis and in 10 patients (4 with complete revascularization and 6 with incomplete revascularization) without these conditions. The sensitivity was 61%, specificity was 63%, positive predictive value was 67%, negative predictive value was 57%, and accuracy was 62%.

Discussion

This study investigated a subgroup of patients with 2- and 3-vessel coronary artery disease treated with PCI, in an attempt to determine the behavior of ETT variables in these patients. Since the ETT is a noninvasive procedure of low operational cost, we also tried to demonstrate the usefulness of this technique as an auxiliary tool for the diagnosis of restenosis and/or new lesions to be used by physicians in clinical practice.

The literature on the value of ETT at late (6 months) follow-up of patients with the same characteristics as our population, treated with multivessel PCI, is scarce since investigators prefer to study myocardial perfusion scintigraphy or pharmacological stress echocardiography, the best methods for a late diagnosis of restenosis, undoubtedly more sensitive and more specific for these cases. Nevertheless, keeping in mind the low cost of ETT compared to these other methods, we decided to undertake a thorough assessment of its variables under various circumstances to obtain as optimal results as possible.

In our study population, PCI resulted in

total revascularization in 35 (42%) patients. In patients with multivessel coronary artery disease it is often impossible to obtain complete myocardial revascularization with PCI because of the unfavorable morphological features of the coronary tree, such as chronic occlusion, twisting and marked calcification. Some relevant studies, such as the Rita (12), Cabri (13) and Bari (14) trials, have shown that in patients with multivessel involvement PCI was not successfully performed in all the vessels with obstructive lesions, thus characterizing incomplete revascularization. Therefore, the outcome of myocardial revascularization through PCI may turn out differently from what was planned, although an incomplete myocardial revascularization may be considered to be functionally complete from the standpoint of anatomy.

Of note, it is important to point out that, even considering the technological development of endoprostheses, the incidence of restenosis within the first 6 months after PCI is still elevated, between 20 and 40% (15,16). Among the patients studied here, the rate of restenosis was 44%, slightly above the value reported in the literature. However, our population was a particular one consisting of patients with multivessel involvement who were treated for up to five lesions, therefore with a higher chance of suffering restenosis. In addition, the procedure in question specifically treats the vessel lesion but does not prevent coronary artery disease from progressing. Our study detected 21 patients (25%) presenting progression of coronary artery disease within the first 6 months.

Serial ETT are common practice in the follow-up of revascularized patients. Comparing the ST segments of the pre- and post-exercise ETT, many investigators have reported that conversion from abnormal to normal results is associated with a high probability of complete revascularization. In our study, 30 patients of 45 with positive pre-PCI tests still remained positive after the

procedure and 20 (67%) of them suffered restenosis and/or new lesion. On the other hand, a significant number of patients still present ST downsloping even after complete revascularization is obtained (17,18). In our study, 33% of patients with a positive ETT did not present restenosis and/or coronary artery disease progression. This can be explained by an abnormality of the coronary reserve and by the presence of an inflammation process that only time can resolve. Zijlstra et al. (19) reported that normalization of the coronary reserve after PCI only occurs weeks or months after the procedure.

On the basis of the present ETT results, there was both a clear reduction of the stress-induced ischemic response (from 45 to 30 patients) and relief from angina (from 27 to 16 patients) 6 months after the procedure, which reflected the improvement of coronary perfusion independent of the therapy used.

In our study population, stress-induced angina was detected in 16 patients during the exercise test carried out after PCI, 4 of them having had all of their diseased vessels treated. However, the absence of angina is not the best criterion for predicting coronary blood flow. Angina in fact disappears with the improvement of coronary perfusion; however, it can also occur in patients with little or no change in myocardial blood flow at all. Hartman (20) also observed that 79% of his patients who had undergone myocardial revascularization were free from angina. This was the case for those with at least one graft patent, which is evidence of the improvement in myocardial perfusion being responsible, to some extent, for the reduction of angina, independent of the patency of the grafts. Holubkov et al. (21) evaluated patients 1 year after PCI and observed that young people and female patients reported more symptoms, as also did those patients with diabetes mellitus, previous myocardial infarction, diseased grafts, and extensive coronary artery disease.

In our study population, systolic blood pressure, rate-pressure product at peak and exercise duration were significantly higher in the ETT after PCI, independent of the results of the latter. Considering that these variables are determinants of myocardial oxygen uptake, we can presume that there was some degree of improvement of myocardial perfusion even in those patients with incomplete revascularization, as well as in those with evidence of restenosis or new lesion after 6 months.

It is well known that the main exercise test parameters with diagnostic, as well as prognostic value after revascularization procedures are: relief from angina, rate-pressure product, normalization of the ST segment, and exercise duration.

Gohlke et al. (22) reported that values of rate-pressure product at peak exercise lower than 25 bpm $\cdot$ mmHg $\cdot$ 10^{-3} were associated with either a poor result or left ventricular dysfunction, and when higher than 30 bpm $\cdot$ mmHg $\cdot$ 10^{-3} they might have been related to complete or sufficient revascularization. In the present study, the rate-pressure product at peak increased significantly after PCI (from 23.8 ± 5.6 to 25.3 ± 5.4 bpm $\cdot$ mmHg $\cdot$ 10^{-3}. However, this variable and systolic blood pressure at peak did not discriminate between patients with and without restenosis or coronary artery disease progression when these two groups were analyzed separately. Probably, these variables are correlated with improvement of myocardial perfusion because restenosis or new lesion usually occurs in one vessel and the size of the ischemic myocardium is smaller than before the procedure. Another possible reason for rate-pressure product and systolic blood pressure at peak not to discriminate the two groups was the use of antianginal medication at the time of ETT. The behavior of these variables was in agreement with other studies (23,24).

The ETT variable which predicted restenosis and/or new lesions in our study popu-

lation was exercise duration, but the same did not apply to a positive test, the presence of angina and rate-pressure product at peak, when these were analyzed separately. With certainty, some patients with antianginal medication at the time of ETT contributed to these findings. Some studies (25,26) have reported that double product, time of tolerance to exercise and heart rate during the postoperative period of myocardial revascularization, when considered separately, are not good predictors of graft patency. Absence of angina and increased functional ability are, however, good predictors when considered in combination (27). A meta-analysis study (28) reported that the sensitivity, specificity and accuracy of exercise electrocardiography for the detection of restenosis after PCI were 46% (33 to 58%), 77% (67 to 86%) and 62%, respectively. In the present study, we found a sensitivity slightly above average (61%), a lower specificity (63.0%) and the same accuracy (62%).

Study limitations

A limitation of the present study is the controversy on the definition of restenosis. Angiographic restenosis is considered to be a continuous variable in large patient populations (29). Even though stenosis with a diameter of >50% has been reported as an appropriate definition of restenosis (30-32), it does not consider factors such as length and geometry of the lesion or endothelial dysfunction, which could cause genuine ischemia. Another limitation is the relatively high rate of submaximal ETT, probably related to drugs. Finally, no additional imaging, echocardiography or myocardial scintigraphy was used with the ETT. On the other hand, our results are specific for patients with preserved left ventricular function, tested without specific drug treatment when possible.

Sequential and comparative analysis of exercise electrocardiography variables before and after PCI permitted us to reach the following conclusions: normalization of the ST segment after PCI usually indicates a successful procedure; increased exercise duration was indicative of permeability of the procedure-related coronaries, with statistical significance (P = 0.008); presence or absence of angina, and the behavior of heart rate, blood pressure and rate-pressure product variables of the ETT after PCI were not good predictors of restenosis and/or new stenosis.

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