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ORIGINAL ARTICLE

Clinical evaluation and stress test have limited value in the diagnosis of in-stent restenosis

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Abstract

Objectives. In-stent restenosis (ISR) is the main limitation of percutaneous coronary interventions (PCI), occurring in approximately 25% of cases. Although frequently asymptomatic, many PCI patients present with recurrent symptoms of chest pain at follow-up raising a clinical suspicion of ISR. The diagnosis of ISR can be challenging in these patients and difficult to rule out without repeat coronary angiography. *Design*. We prospectively investigated the diagnostic accuracy of clinical evaluation and exercise stress testing to detect ISR as compared to coronary angiography, in a consecutive, unselected cohort of PCI patients. *Results*. We studied 91 patients with a total of 143 stents. Clinical evaluation predicted ISR to be likely in 19% of cases and the exercise test was positive in 29%. The binary restenosis rate was 21%. Clinical evaluation had a positive predictive value of 29% and accuracy of 71%, while exercise stress testing had a positive predictive value of 19% and accuracy of 65%. *Conclusion*. In conclusion, we found the diagnostic accuracy of clinical evaluation to be low and not significantly improved by exercise stress testing when evaluating PCI patients for ISR.

Key words: *In-stent restenosis, diagnosis, clinical evaluation, stress test*

One of the main limitations of percutaneous coronary interventions (PCI) with stent placement is the formation of subendothelial hyperplasia and restenosis within or adjacent to the stent (1). This process which occurs in approximately 25% of patients after placement of bare metal stents (BMS) is detected clinically in about 50% of affected patients (2). It has been related to several clinical and angiographic risk factors, but to date no reliable method for predicting ISR is available (3). During follow-up, many patients present with recurrent symptoms of chest discomfort that may raise the suspicion of ISR. Some of these patients will require repeat angiographic evaluation. As the pathophysiological processes underlying ISR differ from those of atherosclerotic coronary artery disease (4), it is not clear whether the same noninvasive diagnostic methods apply (5). We set out to investigate the predictive value of clinical evaluation and exercise stress testing to identify angiographic ISR in a prospective study.

Material and methods

This was a pre-specified sub-study of a larger cohort of patients participating in a trial to evaluate the genetic background of ISR. Patients that underwent PCI with a stent for stable or unstable coronary artery disease were included in a single center prospective study. To be eligible, patients had to be without a previous history of coronary artery disease, impairment in renal function (s-creatinine >130 μmol/l) and any disabling disease preventing them from performing an exercise stress test. After providing informed consent for participation patients were taken to coronary angiography and stent placement at the discretion of the interventional cardiologist. At 6–9 months after the PCI, patients were evaluated clinically and an exercise stress test was performed, to identify prospectively the likelihood of ISR. Thereafter, a quantitative coronary angiography was performed to identify ISR.

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The clinical evaluation was done by an experienced clinical cardiologist (KA) by addressing the following standardized questions:

1. Has the patient experienced any chest discomfort since the coronary angioplasty? (y/n)
   a. If yes, was the discomfort related to exertion or emotional stress?
   b. If yes, was the discomfort relieved by s.l. nitroglycerine or rest?
   c. If yes, was the character of chest discomfort similar to the symptoms he/she had prior to the angioplasty?
   d. Has the patient been hospitalized for chest discomfort since the coronary angioplasty?
2. Are there signs of ischemia on the ECG at rest?

Based on the results of these questions a clinical evaluation was made to estimate the likelihood of ISR in each case. In order for ISR to be considered likely, the answer had to be positive of at least two of the questions 1a–d above and/or one of 1a–d with signs of ischemia on the resting ECG.

The exercise stress test was done by a standardized protocol on bicycle ergometer. For women and elderly men (over 70 years of age) the initial workload was 30 W with increments of 30 W every three minutes. For men 70 years or younger, a starting workload of 50 W was used with increments of 50 W every three minutes. The stress test was continued to exhaustion or until the target heart rate (HR) of 85% of the estimated HR maximum was reached. The test was discontinued in case of severe symptoms, significant ventricular arrhythmia, significant blood pressure drop or ST segment depression greater than 3 mm horizontal in any two adjacent leads. The stress test was considered positive if during exercise, either typical symptoms of angina were provoked or progressive horizontal ST segment depression of at least 1.0 mm in two adjacent leads and these symptoms or signs normalized during the rest phase.

After the stress test, a standard quantitative coronary angiography was performed using the same projections as during the index procedure in each case. The angiographic films were evaluated in a blinded fashion for the presence of binary ISR at TIMI Core lab, Boston, MA, USA. Pre-and post PCI minimal luminal diameters (MLD), follow-up MLD, acute gain, late luminal loss and IRS were calculated. Binary ISR was defined as $\geq$50% diameter stenosis within each stent (1-MLD follow-up/MLD post-PCI)*100. If ISR was present in any one of the stents present, the patient was regarded as having ISR. In addition, the diagnostic value of clinical evaluation and exercise stress test was explored with binary ISR cut-off values of 30% and 70%. Intimal hyperplasia was defined as any luminal loss not reaching 30% within the stent.

The study was approved by the National Bioethics Committee, the Icelandic Data Protection Commission and the Icelandic Radiation Protection Institute.

Statistical analysis

Statistical calculations were performed using SPSS 11.0 (SPSS Inc., Chicago IL) for Windows. All continuous variables are presented as mean+/− standard deviation or proportions as appropriate. Sensitivity (true positive), specificity (true negative), positive and negative predictive values (proportion of patients with positive and negative test results that were correctly diagnosed respectively) were calculated on a per-patient basis. The positive Likelihood ratio weighted by prevalence (post test probability) was calculated as: (prevalence)(sensitivity)/(1-prevalence)(1-specificity). The negative Likelihood ratio weighted by prevalence was calculated: (prevalence)(1-sensitivity)/(1-prevalence)(specificity). A p-value of less than 0.05 was considered to indicate statistical significance.

Results

One-hundred and fourteen patients gave informed consent for participation and entered the study procedures. Subsequently, nine patients withdrew consent and one died. After stent placement, during the 6–9 months preceding the follow-up visit, 13 patients were re-admitted to hospital for chest pain with a clinical suspicion of ISR and had repeat coronary angiograms. These patients were not subject to unbiased clinical evaluation and stress testing was not performed prior to the coronary angiogram. They were therefore excluded from the present analysis leaving 91 patients with a total of 143 stents (range 1–6 per patient). Nineteen (21%) were female and 72 male. The mean age (SD) of the patients was 62 (9.9) years. The prevalence of risk factors and baseline characteristics are shown in Table I. Sixty-five patients (71%) had acute coronary syndromes and 26 (29%) had stable angina pectoris.

The mean diameter of the stents was 3.3 (0.5) mm (range 2.25–4.5 mm) and the mean length was 17.2 (7) mm (range 8–56 mm). Twenty seven percent of the stents were drug eluting (Cypher, Endeavor), the rest were bare metal stents. Sixty patients (66%) received one stent, 15 (17%) had two stents, 13 (14%) had three stents and the remaining 3 (3%) had four to six stents. The stents were placed in the right coronary artery (33%), main stem of the left

Table I. Baseline characteristics and risk factors.

Mean age, years (SD)	62 (9.9)
Male sex, n (%)	72 (79)
Current smoker, n (%)	63 (70)
Hypertension, n (%)	56 (62)
Diabetes, n (%)	12 (13)
Hypercholesterolemia, n (%)	46 (52)
Family history of coronary artery disease, n (%)	66 (79)
Body mass index, kg/m^2 (SD)	28.2 (4.2)
Medication at follow-up,	
Aspirin, n (%)	89 (98)
Clopidogrel, n (%)	32 (35)
Beta-blockers, n (%)	64 (70)
Calcium channel blockers, n (%)	12 (13)
ACE-I, n (%)	21 (23)
ARBs, n (%)	19 (21)
Thiazide diuretics, n (%)	20 (22)
Statins, n (%),	87 (96)

SD: standard deviation, ACE-I: angiotensin converting enzyme inhibitor, ARBs: angiotensin receptor blockers.

coronary artery (1%), left anterior descending branch of the left coronary artery (46%) and circumflex branch of the left coronary artery (21%).

Clinical follow-up was done 210 (49) days after inclusion. Fifty-seven patients (63%) had no symptoms of recurrent chest pain, 29 (32%) had class 2 angina and five (6%) had class 3 angina according to the Canadian Cardiac Society (CCS) score (6). Dyspnea was absent in 57 (63%) of patients, 23 (25%) had New York Heart Association (NYHA) (7) class 2 dyspnea and ten (11%) had NYHA class 3 symptoms. Among the patients with recurrent symptoms, 22 patients (26%) had symptoms of the same character as those that led to intervention. Overall, clinical symptom evaluation raised the suspicion of ISR in 17 (19%) of patients.

The results of the exercise stress test are presented in Table II. Five (6%) patients had inconclusive stress test results, four of these due to inadequate pulse response, one had pacemaker rhythm and two had bundle branch block. Eight (9%) of the patients experienced chest pain during the exercise stress test and 23 (26%) were found to have significant ST segment depression (≥1 mm horizontal) indicating myocardial ischemia, 7 (8%) had ≥2 mm ST segment depression and 1 (1%) had 3 mm ST segment depression. The exercise test was considered positive for ischemia in 26 (29%) of patients at follow-up.

Coronary angiography was performed 7 (9) days after the exercise stress test. The binary restenosis rate per patient (≥50% restenosis) was 21%. The incidence of slight intimal hyperplasia (less than 30%) was 19% and of moderate intimal hyperplasia (30–49% restenosis) was 23%. Among the 19 patients found to have significant ISR, 12 (63%) were asymptomatic.

The sensitivity, specificity, positive and negative predictive values of clinical evaluation to detect binary 50% ISR were 26%, 83%, 29% and 81% respectively. The corresponding values for exercise stress testing were 26%, 71%, 19% and 79% respectively (Table III). The positive predictive value for patients with both clinical evaluation and exercise stress test positive was 17%, it was 19% for the combination of clinical suspicion and negative stress test, 33% if the clinical evaluation was negative but stress test positive and 20% if both clinical evaluation and stress test were negative. The likelihood ratio was 1.53 for a positive clinical evaluation and 0.89 for a negative evaluation. Therefore, the post test probability of ISR for a positive clinical evaluation was 41% (likelihood ratio*ISR rate) and the post test probability of ISR for a negative clinical evaluation was 24%. Similar values were obtained for the exercise stress test; the post test probability of ISR for a positive stress test was 24% and 28% for a negative stress test.

The results of QCA analysis are shown in Table IV. There is no relation between the outcome of clinical evaluation or stress testing and the results of QCA at follow-up. After follow-up angiography, ten patients (11%) needed repeat angioplasty. Three of these were done within 24 hours of the angiography. The median time (range) from angiography to PCI was 24 (0–1032) days. Among the patients needing repeated intervention clinical evaluation was positive in 60% and stress test in 25%.

Table II. Result of exercise stress test.

		Total	ISR	No ISR	p
Duration, mean	minutes (SD)	08:14 (2:04)	08:06 (2:17)	08:15 (2:01)	0.78
Maximal work load, mean	Watts (SD)	142 (44)	133 (43)	144 (45)	0.36
Maximal pulse rate, mean	bpm (SD)	135 (21)	136 (22)	134 (21)	0.781
Maximal HR%,% (SD)		85 (13)	87 (12)	85 (13)	0.53
Pulse increase, mean	bpm (SD)	70 (19)	70 (17)	70 (20)	1.0
Maximal Systolic BP, mean	mmHg (SD)	171 (23)	162 (28)	173 (21)	0.07
Chest pain, n (%)		8 (9%)	4 (21%)	4 (6%)	0.06
Mean ST depression	mm (SD)	1.8 (0.6)S	2.18 (0.8)	1.75 (0.6)	0.21

ISR: in-stent restenosis, SD: standard deviation, HR: heart rate, bpm: beats per minute.

Table III. Diagnostic capability of clinical evaluation and exercise stress test to detect ISR.

	ISR according to angiography at 6–9 months		
	ISR ≥70%	ISR ≥50%	ISR ≥30%
Clinical evaluation			
Sensitivity	4/11 (36%)	5/19 (26%)	7/40 (18%)
Specificity	67/80 (84%)	60/72 (83%)	41/51 (80%)
Positive predictive value	4/17 (24%)	5/17 (29%)	7/17 (41%)
Negative predictive value	67/74 (91%)	60/74 (81%)	41/74 (55%)
Accuracy	71/91 (78%)	65/91 (71%)	48/91 (53%)
Exercise stress test			
Sensitivity	1/11 (9%)	5/19 (26%)	16/40 (40%)
Specificity	55/80 (69%)	51/72 (71%)	41/51 (80%)
Positive predictive value	1/26 (4%)	5/26 (19%)	16/26 (62%)
Negative predictive value	55/65 (85%)	51/65 (79%)	41/65 (63%)
Accuracy	56/91 (62%)	65/91 (71%)	57/91 (63%)

Discussion

ISR is a major limitation of PCI, occurring in approximately a quarter of patients. Although it can lead to severe symptoms of recurrent angina, it frequently remains asymptomatic (8). Many patients are alert to symptoms of chest discomfort after their PCI procedure and present their concerns at outpatient follow-up. One of the main challenges in evaluating these patients is to determine the need for further testing by repeat coronary angiography. Although clinical evaluation of symptoms and conventional exercise stress testing have proven useful in the diagnosis of coronary artery disease, little is known about the usefulness of these methods in detecting ISR (9).

Current guidelines recommend non-invasive stress testing for risk assessment after hospitalization for unstable angina/non ST elevation acute coronary syndromes (10). However, there is less data on screening for ISR. According to the ROSETTA registry (11), routine functional assessment is related to better clinical outcome in patients after PCI. There is however, no consensus on which method of functional testing should be used and the choice depends more on local preference than clinical indications (12).

Although previous studies have investigated the clinical usefulness of exercise stress testing for the evaluation of atypical chest pain in the emergency department (13) and during early follow-up after acute coronary syndromes (14), little evidence is available on the applicability of this method to detect ISR. Most studies to date have used thallium 201 scintigraphy (15,16) or stress single photon emission computed tomography (SPECT) (17), methods that are both more expensive, time consuming and require considerable operator expertise to evaluate. Therefore, for the general cardiologist, it is of value to know how clinical evaluation and exercise stress testing identifies ISR in the clinical setting.

Table IV. Restenosis according to clinical evaluation and stress test.

		No	Yes	p
Clinical suspicion of ISR				
Minimal lumen diameter				
Pre PCI	mm (SD)	0.64 (0.42)	0.66 (0.59)	0.87
Post PCI	mm (SD)	2.57 (0.48)	2.45(0.61)	0.40
Follow-up	mm (SD)	1.88 (0.62)	1.74 (0.89)	0.43
Acute gain	mm (SD)	1.92 (0.59)	1.79 (0.69)	0.41
Late luminal loss	mm (SD)	0.70 (0.61)	0.72 (0.58)	0.92
Restenosis	% (SD)	26 (23)	32 (31)	0.41
Exercise stress test positive				
Minimal lumen diameter				
Pre PCI	mm (SD)	0.64 (0.44)	0.67 (0.48)	0.78
Post PCI	mm (SD)	2.49 (0.50)	2.69 (0.50)	0.10
Follow-up	mm (SD)	1.83 (0.70)	1.92 (0.61)	0.59
Acute gain	mm (SD)	1.86 (0.51)	2.0 (0.82)	0.25
Late luminal loss	mm (SD)	0.67 (0.6)	0.77 (0.60)	0.5
Restenosis	% (SD)	27 (26)	28 (21)	0.87

We set out to evaluate the diagnostic accuracy of clinical assessment and exercise stress testing as non-invasive methods to detect significant ISR in an unselected, prospective population of PCI patients.

The prevalence of ISR 6 months after PCI with stent placement was 19 (21%) in our cohort. The majority of ISR patients (12, 63%) did not have symptoms of recurrent angina. The positive predictive value for symptom evaluation was only 29%, therefore, most patients with recurrent symptoms after PCI do not have ISR. However, the negative predictive value of clinical evaluation is 81%, indicating that the majority of patients without recurrent symptoms do not have ISR. Overall, the diagnostic accuracy of clinical evaluation is 71%.

The exercise stress test showed similar results. The prevalence of a positive stress test was 26 (29%). The majority of ISR patients, (14, 74%) had a negative stress test. The positive predictive value for the stress test was 19%. Accordingly, most patients with a positive stress test did not have ISR. The negative predictive value of stress testing was 79% indicating that the majority of patients with negative stress tests do not have ISR. The overall diagnostic accuracy of exercise stress testing was 62%.

By applying each diagnostic method in logical order, i.e. first clinical evaluation and subsequently an exercise stress test, nothing was gained in diagnostic accuracy. The positive predictive value of having both tests positive was 17%, either one positive resulted in a positive predictive value of 19–33% and if both tests were negative, the likelihood of ISR was still 20%.

No improvement was found in the diagnostic value of these non-invasive tests by using different cut-off values for ISR. One might postulate that a 70% ISR were more likely to cause symptomatic angina or be detected by stress testing. This was not found in the current results. The sample size was too small to be able to identify the optimal cut-off by ROC analysis.

The overall implication of our study is that clinical evaluation and stress testing 6 months after PCI with stent placement has limited value in detecting ISR. Most patients with ISR will have either or both tests negative and the post test probability of ISR for a positive test result is low. Therefore, we concur with current guidelines in concluding that routine stress testing following PCI is of limited value (18). These results are not in contrast to those of the ROSETTA registry (11) which found routine functional testing to reduce the rate of major clinical events at follow-up. As we have not studied the rates of clinical events in our study, we cannot conclude on whether the lack of ISR detection by clinical evaluation and exercise stress testing has any effect on clinical outcome. Indeed, it has been postulated that a certain amount of ISR may even be beneficial to the post-PCI patient.

Study limitations

The main limitation of the present study is its small sample size. The 50% binary ISR rate is only 19% and there is little difference between multiple cut-off values for ISR detection. Also, some of the clinical ISR patients were re-admitted to hospital and had a new coronary angiography before follow-up study procedures could be performed and therefore had to be excluded from the present study. Some of the patients had atherosclerotic disease in more than one coronary artery. Although most of them were fully revascularized during the index procedure, subsequent symptoms and signs of ischemia might well have developed from other vessels than those that were treated by angioplasty. Also, in the case of multiple stents in one patient the identification of ISR in only one of them might be difficult. Finally, newer imaging techniques such as stress echocardiography or nuclear imaging might have detected ISR more accurately than the clinical evaluation and exercise stress test used in this study. These methods, however, are more time consuming, not overall available and rely considerably on operator expertise for interpretation.

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