## Clinical Research

# Stress Testing After Complete and Successful Coronary Revascularization

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## ABSTRACT

**Background:** Noninvasive stress tests play a determinant role in the initial management of patients with chronic angina. Nonetheless, their use in the same patient population is considered inappropriate within 2 years after percutaneous coronary intervention (PCI). Indeed, early abnormal results correlate less well with angiographic control and are attributed to a number of confounding factors. We prospectively assessed prevalence and impact on the quality of life of abnormal stress test results in a highly selected patient population.

**Methods:** Patients with no cardiac comorbidities who underwent successful and complete PCI with stenting for typical angina and had an abnormal exercise stress test (EST) under guideline-directed medical treatment were administered the Seattle Angina Questionnaire (SAQ). Clinical evaluation, EST, and the SAQ were repeated at 1, 6, and 12 months after the index PCI.

**Results:** One hundred ninety-eight patients qualified and were included in the study (mean age, 64 years; 79% men). Although the majority had normal EST results or an increased threshold to angina, at 1 month after the index PCI, 29% of patients still had an abnormal result. At 6 and 12 months, 31% and 29% of patients had abnormal

## RÉSUMÉ

**Introduction :** Bien que l'épreuve d'effort joue un rôle déterminant dans la prise en charge initiale des patients atteints d'angor chronique, l'utilisation de cette méthode non invasive chez ces mêmes patients est considérée comme inappropriée pendant les deux années qui suivent une intervention coronarienne percutanée (ICP). En effet, la corrélation avec l'angiographie de contrôle est moins bonne en cas de résultats initiaux anormaux, qui sont attribuables à divers facteurs de confusion. Nous avons fait une analyse prospective de la prévalence de résultats anormaux à l'épreuve d'effort et de leur incidence sur la qualité de vie chez des patients répondant à des critères de sélection très spécifiques.

**Méthodes :** Des patients ne présentant aucun autre trouble cardiaque, ayant subi avec succès une ICP avec pose d'une endoprothèse pour le traitement d'un angor typique et ayant obtenu des résultats anormaux à l'épreuve d'effort dans le cadre d'un traitement médical conforme aux lignes directrices ont répondu au questionnaire SAQ (*Seattle Angina Questionnaire*). Ils ont été soumis à une évaluation clinique, à une épreuve d'effort et au questionnaire SAQ 1, 6 et 12 mois après l'ICP de référence.

The use of noninvasive stress tests in the diagnosis and prognostic assessment of chronic angina is well established and represents a determinant factor in the selection of the initial treatment strategy.[1-5] In contrast, after coronary revascularization, there is a lack of evidence to support clinical decision making in the same population set. Large clinical trials have consistently reported that many patients present with an abnormal stress test result and persistent symptoms after coronary revascularization.[6-12] Conversely, retrospective observational studies of patients who have undergone revascularization and have repeated testing conclude that despite a relatively high prevalence of abnormal stress test results,

subsequent referrals for coronary angiography and yield for repeated revascularization are low. Therefore, clinical assessment by means of stress testing is considered inappropriate within 2 years after percutaneous coronary intervention (PCI) and within 5 years after coronary artery bypass grafting.[13-18]

However, besides being derived from retrospective analyses, these recommendations seem to express more of a cultural bias that regards as "false positive" any evidence of myocardial ischemia in patients with patent coronary vessels. In such a case, an abnormal result is attributed either to limitations of the noninvasive stress test itself or to patient-related confounding factors, such as incomplete revascularization, hypertension, heart failure, or other comorbidities.

To our knowledge, no prospective study has assessed the prevalence and clinical significance of an abnormal exercise stress test (EST) after PCI and stenting. This study was designed to serially and prospectively assess the prevalence and impact on quality of life of abnormal stress test results and was conducted in a highly selected group of patients, in whom

results, respectively. Quality-of-life assessment by the SAQ showed consistent results, with persistent angina in one third of patients. Control angiography documented a critical lesion, attributable to instent coronary restenosis, in only 8% of patients.

**Conclusions:** When stress testing is systematically performed after PCI, the prevalence of abnormal results is high and is associated with impaired quality of life. Prognostic significance along with the underlying pathophysiological mechanisms of such findings should be investigated.

**Résultats :** Cent quatre-vingt-dix-huit patients répondant aux critères ont été inscrits à l'étude (âge moyen de 64 ans; 79 % d'hommes). Un mois après l'ICP de référence, la majorité d'entre eux présentaient des résultats normaux à l'épreuve d'effort et une élévation du seuil de déclenchement de la douleur angineuse; par contre, 29 % des patients avaient encore des résultats anormaux. Après 6 et 12 mois, des résultats anormaux ont été observés chez 31 % et 29 % des patients, respectivement. Les résultats de l'évaluation de la qualité de vie d'après le questionnaire SAQ ont été constants, indiquant une angine persistant chez le tiers des patients. L'angiographie de contrôle a toutefois révélé une lésion critique, attribuable à une resténose coronarienne dans l'endoprothèse, chez seulement 8 % des patients.

**Conclusions :** Lorsque des épreuves d'effort sont effectuées systématiquement après une ICP, la prévalence de résultats anormaux est élevée et est associée à une diminution de la qualité de vie. Il conviendrait d'étudier la signification pronostique et les mécanismes physiopathologiques sous-jacents de ces observations.

"confounding factors," known to be associated with "false-positive" results, were reduced to minimum.

## Methods

Consecutive patients with typical effort angina (defined as substernal discomfort with a characteristic quality, provoked by exertion or emotional stress and relieved within a few minutes by rest or short-acting nitrate therapy) and an abnormal EST result, despite guideline-directed medical therapy,[19-21] presenting to our clinic in the period from April 2008 through March 2012 were considered for this study. Patients unwilling to participate; those with atypical symptoms (symptoms suggestive of angina, but lacking 1 or more of the typical features of angina), silent myocardial ischemia, congestive heart failure, left ventricular hypertrophy, bundle branch block, valvular heart disease, or previous myocardial infarction; patients receiving digoxin; and those with complete chronic coronary occlusions were excluded from the study. Quantitative lesion assessment (including evaluation with fractional flow reserve for intermediate lesions) and technical details for revascularization were left to the operator's discretion and subsequently reviewed by an experienced investigator (MM). Patients who underwent a complete, successful, and uncomplicated revascularization procedure (defined as a reduction in stenosis diameter to < 10%, with Thrombolysis in Myocardial Infarction flow of 3, no electrocardiographic change, and no residual stenosis in any vessel ≥ 2 mm in diameter) were administered the Seattle Angina Questionnaire (SAQ) and enrolled for follow-up.[22]

Patients repeated the EST and were readministered the SAQ, which measured the qualifying typical angina symptoms, at 1, 6, and 12 months after the index PCI. All patients were maintained under guideline-directed medical therapy during follow-up, unless clinically contraindicated. Those patients presenting with recurrence of symptoms or with worsening symptoms or signs of myocardial ischemia (or both) at any time point were referred for repeated coronary angiography. Patients in whom restenosis was detected underwent repeated PCI and were excluded from further analysis.

EST was conducted using a standard ergocycle ramp protocol (for details, see Supplemental Methods). Two investigators (AH and DM) independently reviewed EST results, and any controversy was resolved with further analysis and discussion.

The SAQ was administered during clinical evaluation. Threshold levels for clinically important differences in each scale were defined as previously described (increases in score of > 8 for physical limitation, > 20 for angina frequency, and > 16 for quality-of-life domains).[23]

Data and results are expressed as mean ± standard deviation or percentages, as appropriate. For details, see Supplemental Statistical Analysis.

## Results

In the period considered (April 2008-March 2012), 1503 patients underwent coronary angiography on an elective basis in our department and were considered for this protocol. Only a minority (198 patients; 13% of the screened population) fulfilled the inclusion criteria and thus were included in the study and enrolled for follow-up (mean age, 64 years; 79% men). At inclusion, all patients were receiving maximum tolerated guideline-directed medical therapy. Of the patients, 63% had hypertension, 67% had dyslipidemia, 34% had diabetes, and 8% were active smokers. Sixteen percent had only 1 risk factor (RF), 29% had 2 RFs, and 55% had 3 or more RFs. At pre-PCI coronary angiography, 81% presented with single-vessel coronary artery disease (CAD 1) and 61% of all lesions were located in the left anterior descending (LAD) artery. All patients underwent implantation with drug-eluting stents (DESs) and received dual-antiplatelet treatment with 100 mg of aspirin and 75 mg of clopidogrel daily for 12 months. Detailed baseline clinical and angiographic characteristics are reported in Table 1. Medications at discharge (baseline) are shown in Table 2.

### Exercise stress testing

At study inclusion, per protocol all patients had an abnormal EST result. One month after the index PCI, overall

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**Table 1.** Baseline characteristics

| Variable | Results | Variable | Results |
|---|---|---|---|
| Male sex | 156 (79%) | BMI | 26.6 ± 3 |
| Hypertension | 125 (63%) | Mean LVEF | 56% ± 5.6% |
| Systolic BP | 125 ± 0.9 mm Hg | 2 risk factors | 57 (29%) |
| Diastolic BP | 68 ± 0.65 mm Hg | 3 risk factors | 109 (55%) |
| Smoking history | 85 (43%) | CAD 1 | 160 (81%) |
| Dyslipidemia | 133 (67%) | CAD 2 | 22 (11%) |
| LDL | 79 ± 1.86 mg/dL | CAD 3 | 16 (8%) |
| Diabetes | 67 (34%) | LAD artery | 121 (61%) |
| HbA1C | 7.2 ± 0.3 | Circumflex artery | 73 (37%) |
| Familial CAD | 91 (46%) | Right artery | 60 (30%) |

Values are expressed as mean values ± standard deviation or as numbers (percentage), as appropriate.

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease (CAD 1 = single-vessel disease; CAD 2 = 2-vessel disease; CAD 3, 3-vessel disease); HbA1c, glycated hemoglobin (%); LAD, left anterior descending; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

there was a significant improvement in workload achievement, with mean values increasing from 79 ± 8.7 W at baseline to 116 ± 6.3 W ($P < 0.05$), 113 ± 5 W, and 118 ± 7.5 W at 1, 6, and 12 months, respectively. There was a similar increase in exercise duration and rate/pressure product (Table 3). However, 57 patients (29%) still had an abnormal EST result. At 6 and 12 months, the percentage of patients with abnormal EST results was 31% and 28%, respectively ($P =$ not significant compared with the first follow-up visit) (Fig. 1). Importantly, of the patients presenting with persistent angina, the majority had an increased threshold to angina, whereas only a minority presented with worsening symptoms.

## Quality of life

At baseline, the study population had moderate physical limitation caused by angina and therefore perceived their quality of life to be quite limited. At the 1-month follow-up, there was a significant increase in the scores for all the 5 SAQ domains, with no further significant change at the 6- and 12-month follow-up visits (Supplemental Table S1). However, 1 month after PCI, about 30% of patients had persistent angina, resulting in a worse quality of life compared with those with no angina (Fig. 2). Compared with patients with symptom resolution, worse quality of life in patients with persistent angina was mainly determined by angina recurrence during moderate to intense activity such as running or jogging, nitroglycerine use, and health-related worrisome thoughts.

**Table 2.** Discharge treatment

| Medication | Result |
|---|---|
| β-Blockers | 143 (72%) |
| ACEI/ARB | 147 (74%) |
| Statin drugs | 186 (94%) |
| Antiplatelet drugs | 198 (100%) |
| Nitrate drugs | 135 (68%) |
| Calcium channel blockers | 67 (34%) |

Values are expressed as numbers (percentage).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

**Table 3.** EST results

| Variable | Baseline | 1 mo | 6 mo | 12 mo |
|---|---|---|---|---|
| Workload (W) | 79 ± 8.7 | 116 ± 6.3 | 113 ± 5 | 118 ± 7.5 |
| Exercise duration (min) | 7.3 | 9.4 | 9.7 | 10.1 |
| Peak rate-pressure product/1000 | 22.2 ± 3.5 | 25.7 ± 2.4 | 24.9 ± 4.3 | 26.1 ± 2.8 |

Data are presented as median or percentage when indicated. Peak rate-pressure product/1000 expressed in beats × mm Hg/min.

EST, exercise stress test.

## Angiographic data

Patients with a persistent abnormal EST result and impaired quality of life (a total of 67 patients during the 1-year follow-up) underwent repeated coronary angiography at a median of 7 ± 2 months from the index PCI. At coronary angiography, there was no significant progression of athero-sclerotic disease; however, 16 patients (8% of total population) had an in-stent restenosis that could explain the persistence of angina and abnormal EST results, and these patients were thus were excluded from further analysis. In 12 patients, the restenosis developed within 6 months of the index procedure. Overall results are summarized in Supplemental Figure S1.

## Discussion

The main finding of this study is that when systematically assessed, a considerable number of patients present with an abnormal EST result and angina after complete and uncomplicated PCI. Accordingly, as assessed by means of the SAQ, these patients complain about impaired quality of life. The prevalence of persisting angina and inducible ischemia after PCI largely exceeds the restenosis rate.

The findings of our study are consistent with previous large clinical trials that have reported that many patients with
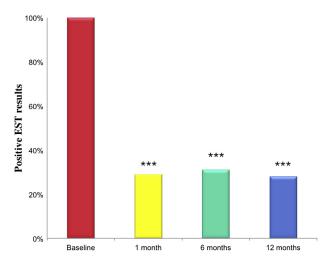


**Figure 1.** Exercise stress test results. Patients (expressed in percentage) presenting with abnormal stress test results at baseline (**red**) and at 1-month (**yellow**), 6-month (**green**), and 12-month (**blue**) follow-up visits after percutaneous coronary intervention (***$P < 0.01$ vs baseline).
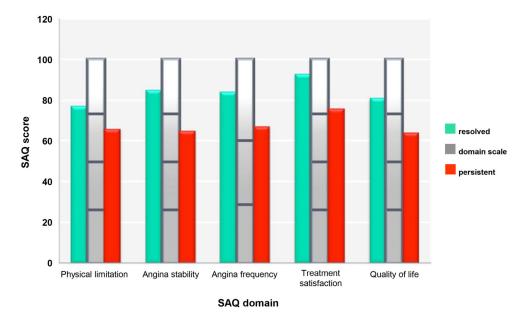
**Figure 2.** The Seattle Angina Questionnaire (SAQ) results at 1 month after index percutaneous coronary intervention (PCI). Results of the 5 domains of the SAQ in patients with resolved symptoms (**green**) vs patients with symptom recurrence (**red**) at 1 month after index PCI. The central column represents the scale for each domain, ranging from 0-100, subdivided into areas of clinically meaningful differences. Values are expressed as mean scores.

angina present with abnormal stress test results and complain about angina symptoms after coronary revascularization.[6-12] However, being that these studies were designed to investigate other end points, abnormal test results have usually been discounted and attributed to a combination of procedure-related factors (eg, restenosis, incomplete revascularization), patient-related factors (eg, left ventricular hypertrophy, aortic valve disease), and the diagnostic inaccuracy of the noninvasive stress testing tool. Our study was specifically designed to prospectively assess the prevalence and the clinical correlates of an abnormal EST result in a highly selected group of patients undergoing PCI, excluding conditions known to interfere with electrocardiographic interpretation. Only patients with complete coronary revascularization were included in the study. Patients with complicated or unsuccessful (or both) or suboptimal procedural results and those with total chronic occlusion were also excluded per protocol.

In most series, the reported restenosis rate after DES implantation is < 10% and usually occurs 2-3 months after the index PCI.[24-27] Accordingly, in this study, 16 (8%) patients had recurrent angina and ischemia attributable to restenosis. These patients underwent repeated PCI and were therefore excluded from further analysis. Progression of atherosclerotic disease in native coronary arteries did not contribute to a significant extent to persistence of symptoms in this series. Yet, one third of patients presented with a persistent positive stress test result.

Noninvasive testing is a well-established strategy for the management of patients with chronic angina; abnormal test results or high-risk features, or both, are determining factors for establishing the need for coronary angiography and revascularization in patients with suitable coronary anatomy.[2] Conversely, the use of noninvasive testing after revascularization in the same patient population has been performed but is not properly defined and varies widely among centres.[28,29]

Indeed, there is some evidence of high rates of abnormal results with low angiographic yield (ie, a patent coronary artery) so that their routine use has been strongly discouraged in the first 2 years after PCI and 5 years after coronary artery bypass grafting.[13-18,30] In clinical practice, a noninvasive stress test is rated as a "false positive" when no CAD is detected at coronary angiography. Accordingly, we should have regarded as "false positive" the EST results in 51 patients in this series. However, in our study, an abnormal EST result was consistently associated with persistent angina and impaired quality of life. In line with these considerations, the few studies that investigated the role of stress testing in patients after revascularization have suggested that persistence of ischemia is associated with worse clinical outcomes in this population also.[31-34] Nonetheless, conclusions about prevalence and clinical significance are difficult to draw from these studies; besides using different time points for evaluation, not all of them adopted baseline stress test results for comparison during follow-up and not all of them excluded patients with incomplete revascularization or other factors that could affect the results. In our study, we made an effort to negate these limitations by adopting identical and serially repeated clinical evaluation (including exercise stress testing and administration of the SAQ) both at baseline and at early (1 month), medium (6 months), and long-term (12 months) time points after the index PCI. In addition, by excluding patients with incomplete revascularization and those with other confounding factors for abnormal results, we increased the probability for obtaining highly reproducible and reliable stress test outcomes. To the best of our knowledge, this is the first study to systematically assess the prevalence and clinical significance of abnormal EST results in consecutive patients undergoing *complete* and *uncomplicated* PCI.

In our study, the majority of patients had prompt relief from angina and significantly improved their exercise

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tolerance after PCI. Conversely, only one third of patients reported minor or no benefit from the procedure. As recently documented by Li et al.,[35] microvascular dysfunction can be the cause of recurrent angina in patients with obstructive CAD who were treated with PCI. Other hypothesized mechanisms include endothelial dysfunction, inflammation, platelet dysfunction, coagulation abnormalities, and various combinations of these factors.[36] In contrast, the literature suggests that the presence of obstructive CAD does not imply ischemia precipitation or vice versa.[36-38] In line with these considerations, our findings suggest that factors responsible for ischemic syndromes in the absence of obstructive CAD may also play a relevant role when obstructive CAD is present. Under these circumstances, removal of stenoses by PCI and repeated stress testing may unmask the presence of these mechanisms and thus explain the lack of benefit from PCI in all patients.

### Practical implications

Chest pain and evidence of myocardial ischemia have a significant impact on quality of life and potentially on prognosis.[37] However, patients who have undergone revascularization and have recurrent angina have already received what currently is considered the "state of the art" treatment and thus may be further overlooked. Our study population underwent complete revascularization, and there was little chance to further intensify medical treatment (Table 2). Nonetheless, systematic testing showed that a considerable number of patients have persistent angina. We believe that acceptance and correct identification of this patient subset represents the first step toward a better understanding and management of the disease. In this regard, systematic testing would represent a cheap and easily available tool when persistent angina is suspected clinically. For instance, unnecessary and expensive therapeutic strategies can be avoided in patients in whom obstructive CAD is not the cause of myocardial ischemia. Alternatively, recommendations for the addition of drugs that could potentially affect outcomes, such as ranolazine and ivabradine, have emerged since the completion of our study.[20]

### Study limitations

This study was not designed to investigate the prognostic implications of an abnormal EST result after PCI. In addition, the small number of patients does not allow us to draw a meaningful correlation between baseline characteristics and EST results. Serial testing, however, unlike initial or 1-time testing, has more stringent requirements and is subject to variability because of technical, procedural, interpretational, and biological factors. Moreover, an invasive assessment of pre- and post-PCI coronary flow reserve or use of imaging tests would have been useful in identifying possible mechanisms of persistent ischemia (ie, microvascular dysfunction). However, the observational characteristic of the study and the purpose of assessing the prevalence and clinical correlates of abnormal stress test results, together with ethical and economic considerations, prevented us from including such measurements in the study protocol. Finally, we sought to overcome these difficulties by including a highly selected patient population and by adopting a widely available and low-cost tool such as the clinical visit with exercise testing.

### Conclusions

This study documents a high rate of abnormal results in patients undergoing serial noninvasive stress testing after revascularization with PCI and stenting. These results largely exceed restenosis rate, correlate with a poor quality of life, and given the highly selected patient population, cannot be attributed to confounding factors such as patient- or procedure-related factors. Before banning early assessment with stress testing, the prognostic significance along with the underlying pathophysiological mechanisms of such findings should be investigated.

### Disclosures

The authors have no conflicts of interest to disclose.

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## Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2015.12.025.