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Early exercise stress testing is safe after primary percutaneous coronary intervention

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Abstract

Background: The optimal timing of exercise stress testing post primary percutaneous coronary intervention is uncertain with anecdotal evidence suggesting an increased risk of acute myocardial infarction and/or death if performed too early. This has translated into a delayed return to normal life activities following an acute myocardial infarction resulting in an increase in socio-economic burden.

Aims: We hypothesize that early (within 7 days of primary percutaneous coronary intervention) exercise stress testing is safe.

Methods: A prospective study of consecutive patients enrolled into the Cardiac Rehabilitation Program at a tertiary referral centre that underwent primary percutaneous coronary intervention, and who were able to perform a treadmill stress test were recruited. Timing of exercise stress testing was within 7 days post primary percutaneous coronary intervention and outcomes of death, acute myocardial infarction and other major adverse cardiac event were assessed 24 hours post exercise stress testing.

Results: Recruited patients (n=230) aged between 29 and 78 (mean age 56 ± 10 years) with 191 being males (83%) and 39 being females (17%). While 28 patients had a positive stress test (12.2%), there were no deaths, acute myocardial infarction or any other major adverse cardiac event within 24 hours of performing the exercise stress testing. Mean METS achieved were 8.1 ± 2.3.

Conclusions: Early exercise stress testing after primary percutaneous coronary intervention appears safe.

Keywords

Acute myocardial infarction, STEMI, primary percutaneous coronary intervention, exercise stress test

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Introduction

A multitude of studies, all of which utilised data from the pre-thrombolysis and thrombolysis eras, clearly demonstrated the safety and functional benefits of exercise stress testing (EST) following acute myocardial infarction (AMI).[1, 2] In addition to its ability to guide therapy, EST incorporation into risk stratification 1 week after AMI, was shown to allow the safe and early return of patients to normal activities including work at 2 weeks[3].

In the current era of primary percutaneous coronary intervention (PCI) however, the safety of early EST following primary PCI is not clear. Firstly, there have been multiple anecdotal reports of stent thrombosis induced by EST.[4-6] Secondly, while a DANAMI-2 sub-study of primary PCI did not report any adverse events secondary to pre-discharge EST's, there have been many changes in AMI therapy over the subsequent 10 years.[7]

Consequently, timing of EST after primary PCI is now dependent on the personal preferences of treating cardiologists and/or institutional guidelines. The aim of this study

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was to assess the safety of early (≤7 days) EST following primary PCI.

Methods

Patients

Data was prospectively collected for all patients presenting between July 1998 and May 2010 inclusive.

All patients were administered pre-procedural aspirin (150mg), post-procedural aspirin (100-150mg daily) indefinitely, and clopidogrel (75mg daily) for a minimum of one month for bare metal stents and a minimum of 3 months for drug eluting stents. Intravenous heparin and abciximab were administered prior to lesion intervention and continued for 24hrs as an infusion. Beta blockers, angiotensin-converting enzyme inhibitors, and statins were used at the discretion of the treating cardiologist. All patients received education and counselling from medical and nursing staff during their hospital stay and they attended 3 lecture and discussion sessions about risk factor modification, optimum diet, and medications.

Inclusion/Exclusion Criteria

Patients were considered for inclusion if they had had a STEMI that was treated with primary PCI at Westmead Hospital and were enrolled into the cardiac rehabilitation program at Westmead Hospital. STEMI was defined as chest pain in the presence of ST elevation >1mm in 2 consecutive ECG leads at presentation and an occluded coronary artery on angiography. Patients were excluded if they were unable or unwilling to perform the treadmill EST or if their treating cardiologist refused EST within 1 week post STEMI. For these patients, a deferred (>7 days) EST was offered.

Exercise Stress Testing

Symptom and sign limited nurse supervised treadmill exercise testing was performed as described by Zecchin et al., using either Bruce, modified Bruce, or modified Naughton protocols.[8] Stress tests performed ≤7 days post STEMI were classified as early, while stress tests performed >7 days were classified as deferred.

Prior to stress testing the supervising nurse reviewed the patient's medical history, medication use, and risk factor profile, provided accurate information to facilitate informed consent for the procedure, and carried out physical assessment including groin checks, baseline haemodynamics, 12 lead ECG's, and chest and heart auscultation.

Systolic blood pressures were measured by an aneroid sphygmomanometer at 1-minute intervals and heart rate and rhythm was recorded on a computerized 12-lead stress test analyzer (CASE System, GE Medical Systems Information Technologies, Inc. Milwaukee, WI).

Exercise tests were considered positive for ischemia if there were ≥1mm ST-segment depression or ≥2mm ST-segment elevation, 80ms after the J point in 3 consecutive QRS complexes on any lead, or if the patient developed chest pain with exercise. If none of these events occurred and the maximal heart rate achieved was less than 70% of predicted (220 - age), the test was considered indeterminate.

Criteria for test termination included maximum predicted heart rate achievement, systolic blood pressure >220 mmHg, diastolic blood pressure >110 mmHg, an ischemic ST segment response of 4 mm of horizontal or downsloping ST-segment depression 80 ms after the J point, or 4 mm ST-segment elevation in 1 or more leads, chronotropic or inotropic incompetence, initiation of new QRS morphologic features such as left or right bundle branch block, broad or narrow complex tachyarrhythmias, atrioventricular nodal block, or patient request to stop because of anxiety, dyspnoea, fatigue, leg claudication, presyncope, increasing chest discomfort, and perceived excessive speed of treadmill.

Outcomes

All patients undergoing EST where followed up via a nurse initiated phone call at a minimum of 24 hours following EST. Endpoints of death, AMI, and major adverse cardiac events (MACE) during or within 24 hours of exercise stress testing were recorded and analysed independently.

Statistics

Data is expressed as percentages or means ± standard deviations for nominal and continuous data respectively. Chi-square tests were used to assess significance of nominal data, while Mann-Whitney U and Kruskal–Wallis one-way ANOVA tests were used for continuous data. Significance was defined as $p<0.05$. All statistical analyses were performed using SPSS version 18.

Results

Out of a total of 689 consecutive patients that underwent primary PCI and were enrolled into the cardiac rehabilitation program at Westmead Hospital between July 1998 and May 2010, 230 performed early (≤7 days) and 443 performed deferred (>7days) treadmill stress testing. EST was not performed in 16 patients due to mobility limitations. Demographics, PCI data, and EST results are listed in Table 1. Importantly, all patients were taking aspirin and clopidogrel at the time of EST.

Patients that were offered deferred (>7days) treadmill stress testing had a higher rate of drug eluting stent use, greater multi-vessel stenting, longer total stent lengths, and more positive stress tests compared the early (≤7 days) group.

The main reasons for stress test termination were dyspnoea (58%), fatigue (24%), angina (9%), systolic blood

Table 1. Demographic, PCI, and EST characteristics of early and deferred EST groups.

Baseline variables	Early EST (*n*=230)	Deferred EST (*n*=443)	Significance (*p* value)
Mean age (years)	56 ± 10	56 ± 11	0.92
Male gender (%)	83	88	0.06
Body mass index	28 ± 4.3	28 ± 4.5	0.33
Diabetes (%)	19	22	0.16
Smoking (%)	41	43	0.30
Beta blocker (%)	78	75	0.27
Abciximab (%)	65	77	<0.01
Multivessel disease (%)	53	47	0.10
>1 vessel stented (%)	2.6	7.4	<0.01
>1 stent used (%)	26	31	0.09
Total stent length per patient (mm)	22 ± 10	25 ± 14	0.05
Mean stent diameter (mm)	3.1 ± 0.9	3.1 ± 0.6	0.67
Drug eluting stents (%)	10	35	<0.01
LVEF (%)	49 ± 11	50 ± 11	0.06
Time to EST (days)	4.9 ± 1.4	21.4 ± 14.6	<0.01
% of PredMax HR achieved	84 ± 11	84 ± 13	0.93
METS achieved	8.1 ± 2.3	8.3 ± 2.7	0.79
Positive test (%)	12.2	5.6	<0.01

LVEF, left ventricular ejection fraction; mm, millimetres; b.p.m, beats per minute; PredMax, Predicted Maximum; HR, heart rate

Table 2. Data of published anecdotal cases of stent thrombosis following EST.

Authors (reference)	Age	Sex	PCI type	Vessel	Stent used	Post PCI therapy	PCI to EST time	EST result	EST to THR Time
Connelly et al.	49	M	Non-primary	LAD	ACS Duet Stent	Aspirin & Ticlopidine	840h 0m 0s	negative (during stress phase)	5 minutes (into recovery)
Parody et al.	75	M	Primary	LAD	Carbostent	Aspirin & Clopidogrel	6 months	negative	0h 3m 0s
Meurin et al.	40	M	Non-primary	LAD	Not Mentioned	Aspirin & Ticlopidine	264h 0m 0s	negative	0h 30m 0s
Meurin et al.	36	M	Primary	RCA	Not Mentioned	DNR	360h 0m 0s	negative	0h 30m 0s

LAD, left anterior descending artery; RCA, right coronary artery; DNR, details not reported; THR, thrombosis

pressure drop of 20mmHg (1.3%), musculoskeletal pain (3.1%), technical reasons (2.2%), and patient request (0.9%).

The endpoints of death, AMI, and MACE did not occur in either group within this study.

Discussion

The main finding of this study was the absence of adverse events within 24 hours of performing an early EST after primary PCI. These results suggest that EST within 7 days of primary PCI is safe, extending the findings of Valeur et al. (DANAMI-2 sub-study) to the current era of primary PCI.[7]

Although Valeur et al. reported no adverse events following early EST after primary PCI, a study of EST safety 1 day after non-primary PCI by Roffi et al. reported a 0.2% acute and 1% subacute rate of stent thrombosis. No events occurred however, within the critical 24 hours following EST's performed 1 day post PCI.[9] This suggests that the absolute risk of stent thrombosis secondary to an early EST was far smaller than those of established risk factors following non-primary PCI.

Established risk factors for stent thrombosis include diabetes, poor left ventricular function, primary PCI, stent length, stent diameter, drug eluting stent use, and medication compliance[10]. Comparison of risk for stent thrombosis between our study and both Valeur et al. and Roffi et al. was limited however. While patients in our study had similar left ventricular ejection fractions, higher rates of diabetes, and achieved higher EST workloads, PCI characteristics were not disclosed by Valeur et al. to allow a full comparison of stent thrombosis risk. Although Roffi et al. had similar mean stent diameters to our study, PCI was performed in a non-primary setting, mean total stent length was shorter, and glycoprotein IIb/IIIa use was lower.

Review of anecdotal reports of stent thrombosis following EST revealed 4 cases of stent thrombosis after PCI and

are summarised in Table 2.[4-6] Of these, only 2 cases had received a primary PCI, but neither underwent early (≤7 days) EST. One primary case did undergo relatively early (15 days) EST, although post PCI anti-platelet therapy for this patient was not reported.

Evidence to support an augmented pro-thrombotic state secondary to exercise following myocardial infarction in adults is complex with studies demonstrating activation of both coagulation and fibrinolytic systems for periods of up to 24 hours after exercise and for periods of up to 3 months after myocardial infarction.[11-13] Given the demographics of our study population, exercise induced platelet and coagulation activation was likely to be greater than that of the fibrinolytic system. The lack of stent thrombosis despite this effect suggests that an exercise induced pro-thrombotic state requires the presence of established major risk factors for stent thrombosis before thrombosis is precipitated.

Relative influences of risk factors on stent thrombosis risk vary from patient to patient. The absolute risk from factors other than stent exposure should remain static until dual anti-platelet therapy is changed to monotherapy whence it should rise. Although risk from stent exposure is highest earlier on, it is at this time that abciximab related glycoprotein IIb/IIIa receptor blockade is greatest. Such blockade can be detected up to 15 days after cessation of abciximab.[14]

Time to revascularisation is an independent predictor of morbidity and mortality of an acute ST elevation myocardial infarction.[15] Hence the performance of an early inpatient EST is likely to be safer compared to a delayed EST in an outpatient setting.

The other benefits of early (≤7 days) EST are well established. Firstly, it may be incorporated into a risk stratification protocol to determine appropriateness for early return to work.[3] Secondly it allows identification of patients with a poorer prognostic outlook. Lastly, it enables early assessment of the functional significance of residual coronary artery disease.

While there is no current accepted safe period of EST following primary PCI most cardiologists would opt not to perform an EST within a 4 to 6 week period following primary PCI as it is deemed to carry an increased risk of stent thrombosis. Our study not only clearly demonstrates that performing an EST post primary PCI is safe, but can be performed within 7 days of a primary PCI without any adverse outcome.

The main limitation of this study was its prospective observational design combined with its reliance on the personal preferences of treating cardiologists for enrolment. Hence out of a total of 689 STEMI patients undergoing cardiac rehabilitation at Westmead Hospital, only 33% underwent an early EST. However, although the mean time to EST and risk factor profile between early and deferred groups were different, the mean time to EST within the deferred group was still relatively early (<6 weeks).

Conclusion

Early (≤7 days) exercise testing after primary PCI appears safe and may provide a simple, safe and economical alternative to assessment of prognosis and function following a primary PCI. This would prove invaluable at a time of such global financial uncertainty.

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