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IMPORTANCE OF THE EXERCISE TEST FOLLOW-UP PROGRAMME FOR PATIENTS WITH CORONARY ARTERY DISEASE WHO UNDERWENT PERCUTANEOUS CORONARY INTERVENTION

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The clinical course and prognosis of coronary heart disease (CHD) can be modified favourably with percutaneous coronary intervention (PCI) in combination with medication. A follow-up programme was developed in the Latvian Centre of Cardiology, which included a stress electrocardiogram for patients after PCI. This is the first study in Latvia, and provides wide opportunities to evaluate functional status of patients, treatment effectiveness, possible risks and prognosis after PCI. Exercise tests are widely used for the evaluation and diagnostics of CHD. This method has been successfully implemented in diagnostics of restenosis in coronary arteries, a process which pathophysiologically differs from primary atherosclerosis. A total of 7,300 patients with CHD were followed-up in one year after PCI. An exercise test was conducted one, three, six and twelve months after PCI. Clinical and functional status of patients and risk of restenosis were evaluated and corrections in medications were made. Seventeen percent of patients had chest pain and 13% had significant ST-segment changes in electrocardiogram. Restenosis of coronary arteries in angiography were established in 6.4%. In half of those patients above restenosis was diagnosed early — three to six months after PCI. We established a patient subgroup (22%) with "silent" ischemia (positive exercise test without chest pain), out of whom 41% had restenosis. For left main (LM) disease patients 50% of all restenosis diagnoses also were diagnosed early (three to six month after PCI). Restenosis was associated with ST-segment deviation in the exercise electrocardiogram. A lower Robinson index (RI) was registered in the same group of patients. A focussed follow-up programme performing exercise test allows to determine timely possible risk of restenosis, to adapt medication doses, to reduce risk factors and to influence positively patients' compliance.

Key words: *coronary heart disease, percutaneous coronary intervention, restenosis, exercise test.*

INTRODUCTION

In Latvia, there is a heavy burden of coronary heart disease (CHD), which still remains the leading cause of death in our country. Priority is given to patients with established CHD because they are at high risk of further cardiovascular morbidity and mortality (Fletcher *et al*., 1995). CHD management consists of interventional as well as therapeutic treatment. Since the implementation of interventional treatment restenosis appeared as a new challenge for cardiologists. Restenosis pathophysiologically differs from primary atherosclerosis (backward contraction, late remodulation, thrombosis, neointimal proliferation), which makes it competitive for cardiovascular diagnostics (Libby and Theroux, 2005). Only one-third of patients with restenosis have typical complaints like angina pectoris under physical exercise. Almost half of the patients with restenosis have asymptomatic ST-segment changes in electrocardiogram during physical test (silent ischemia) (Bengston *et al*., 1990; Ruygrok *et al*., 2001). Those patients have very high risk of coronary events, which adds special importance to early diagnosis of possible restenosis (Eisenberg *et al*., 2001; Babapulle *et al*., 2007). A standard method in CHD diagnostics and follow-up is an exercise test, which remains the most available and cost effective diagnostic opportunity (Kligfield and Okin, 1994; Kligfield and Lauer, 2006). Even though the clinical value of solitary exercise test nowadays is limited (Gianrossi *et al*., 1989), our observations showed that focussed exercise test programmes could be useful in early diagnosis of restenosis.

From the very beginning after introduction of interventional treatment in coronary artery disease in the Latvian Centre of Cardiology, a specific follow-up programme with consecutive aims was developed:

1) to evaluate functional status of patients after interventional treatment, possible risks of further cardiovascular events and effectiveness of actual treatment;

2) to develop a prognostic model that can identify patients with unfavourable long-term prognosis or inadequate interventional treatment results;

3) to identify a patient data set to analyse specific subgroups of patients at different risk of further cardiovascular events.

MATERIALS AND METHODS

The exercise tests investigation of 7,300 patients were analysed from the year 2006 till 2008. Patients were inspected 1–3; 3–6, 6–12 and 12–24 months after interventional treatment by a physical stress test to evaluate possible risk of restenosis and to perform adequate corrections in medications. We used a bicycle test with standardised protocol developed in the Latvian Centre of Cardiology, which excluded inter-operator influence on results and determination of formulation variability. We assumed that the exercise test was positive if in electrocardiogram (ECG) appeared horizontal or downward sloping ST-segment depression or elevation ≥1mm up to 60 ms after the QRS, in particular when ECG changes were accompanied with typical chest pain at loud of 75 Watt and lower and continued more than 3 min after end of the load (Mintāle and Ērglis, 2008). We analysed also haemodynamic parameters — maximal heart rate, systolic blood pressure, Robinson index (RI), total exercise time, chronotropic competence as well as subjective data — exercise induced angina pectoris, exercise limiting symptoms and time interval to the beginning of angina pectoris.

In the framework of the follow-up programme, analyses of drug therapies were conducted for 3,200 patients at three, six and twelve months after interventional treatment. The control group consisted of 382 patients without a focussed follow-up programme. For the control group patients a drug therapy check was performed twelve months after percutaneous coronary intervention (PCI). Adequate corrections in drug therapy and risk factor control were made depending on exercise test results.

The Latvian Society of Cardiology recommendations on stable angina pectoris (Erglis *et al*., 2007) have set goals for use of appropriate drug therapies, which include antiplatelets, lipid lowering drugs, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), β-blockers and calcium channel blockers.

The aim of the programme was not only to evaluate functional status of patients after interventional treatment but to assess treatment efficacy and to perform changes in medications depending on data received in exercise test. Therefore, we analysed the used drug groups. Separate analyses were made in high risk patients with left main (LM) disease. SPSS 12.0.1. version was used for statistical analyses. Baseline characteristics were summarised as frequencies and percentages for categorical variables and as means and SDs for continuous variables. Analyses were performed using the Student *t* test/ANOVA method for continuous variables. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Serious complications such as myocardial infarction, life threatening arrhythmias or death did not appear during the exercise test. Coronary complaints were admitted by 1,226 (16.8%) patients and ischemic ST-segment changes were documented in 975 (13.4%) patients. Generally, from whole study group angiographic diagnosis of restenosis was diagnosed in 470 (6.4%) patients (Fig. 1).

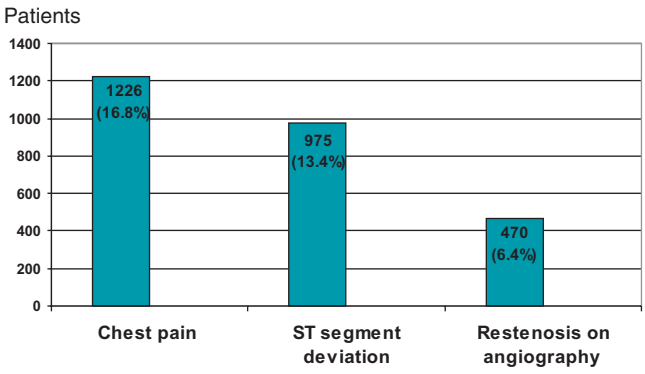

Fig. 1. Total exercise test results.

During follow-up visits, we identified a special patient subgroup (22% – 1,606 patients) without chest pain but with a significant shift of the ST-segment in ECG during physical loading. This is called silent ischemia and is connected with unfavourable prognosis (unstable angina, myocardial infarction, cardiac death). Relevant restenosis on angiography was established in 658 (41%) patients with silent ischemia, which amounts to 9% of all patients. The large proportion of patients with silent ischemia demonstrates the necessity of a focused follow-up programme instead of complaint based indication for the exercise test.

Patients with a focussed follow-up programme almost achieved drug therapy goals set by national guidelines (Fig. 2). The reported use of drug therapies 12 months after PCI in control group patients significantly decreased. Reduction in use of aspirin, statins, β-blockers, ACE-inhibitors, clopidogrel and Ca channel blockers was recorded in 12%, 16%, 5%, 11%, 29% and 33%, respectively (Fig. 3). The majority of dose corrections were made 3–6 months after intervention for adequate blood pressure control (for 46% of patients) and 6–12 months after PCI for achievement of cholesterol targets (for 72% of patients).

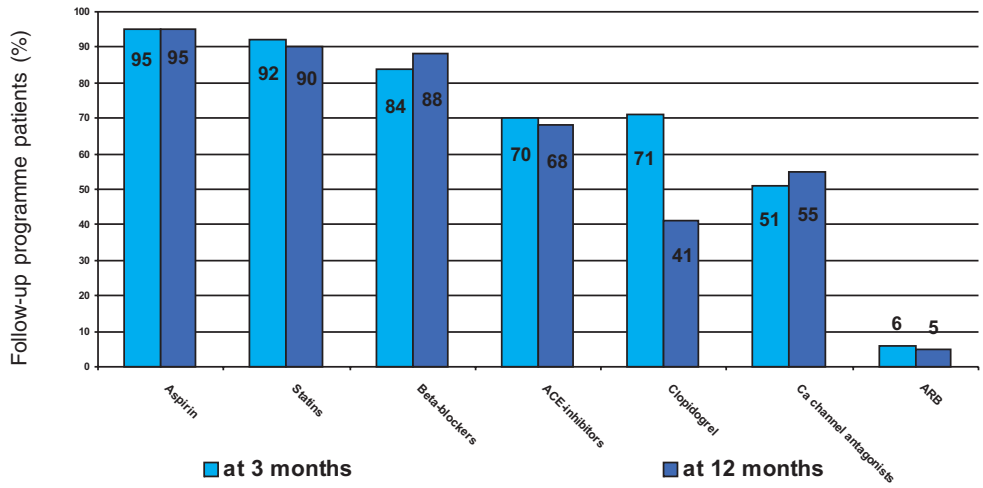

Fig. 2. Drug therapy analyses for follow-up programme patients.

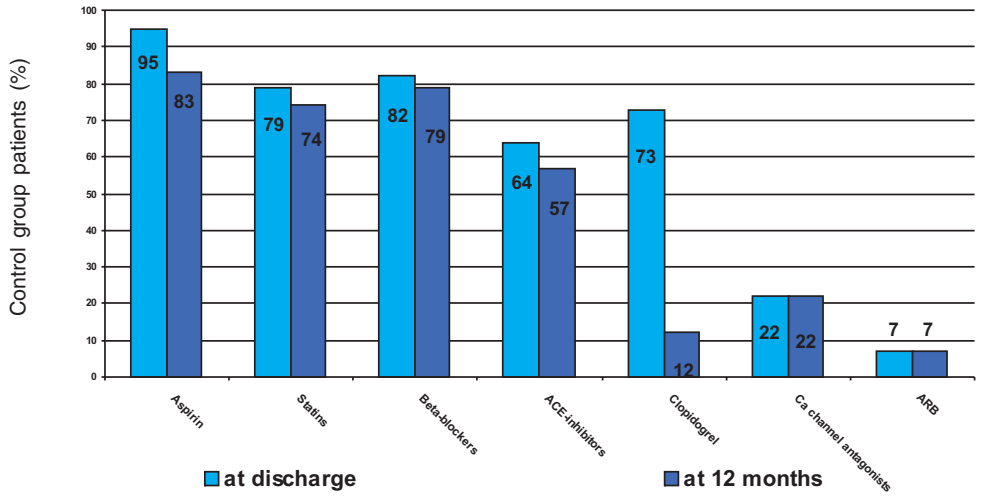

Fig. 3. Drug therapy analyses for control group patients.

Separate analyses were conducted for high risk patients with LM disease after successful interventional treatment with implantation of drug eluting stents. In those patients 50% of all restenosis were diagnosed early (3 to 6 months after PCI), 47% in the time interval between 6 to 12 and the others 7% twelve to 24 months after PCI. In the early exercise test follow-up visit (one to three months after PCI) documented ischemic changes on ECG correlated tightly with angiographic results at 1–3 months after PCI. Each restenosis documented on angiography was accompanied with ST-segment depression on exercise ECG. The calculated specificity was 100% and sensitivity 29% for the exercise test at early follow-up (1–3 months after PCI). In this subgroup a lower RI was registered. The follow-up results at 3–6 months after PCI showed a ST-segment shift correlation with angiographic restenosis. Calculated specificity was 86% and sensitivity 50%. Every patient with newly developed lesions in other coronary vessels documented on angiography 3–6 months after PCI had ST-segment depression at early follow-up. However, for patients without stenosis on angiography in 92.9% of cases ST-segment changes on exercise ECG were not documented. This corresponds to a sensitivity of 33% and specificity of 93%.

Patients with restenosis achieved less physical loading at exercise test because of test termination without reaching submaximal heart rate according to shift of the ST-segment. This could explain the differences in RI curves for patients with and without restenosis. However, there were no statistical differences in maximal heart rate and systolic blood pressure between patients with and without restenosis (Table 1). For patients with restenosis the RI showed a significant decrease at 3–6 months after intervention (209.80 ± 59.58 in comparison with 226.19 ± 60.01 at early visit) (Table 2). In contrast, for patients without restenosis, the RI demonstrated a significant increase from 210.79 ± 52.90 (1–3 months after PCI) to 225.03 ± 46.41 (3–6 months after PCI) and at 6–12 months after PCI reached a plateau (222.00 ± 47.44) (Table 3). Although there was no statistical significance ($P > 0.05$), a graphical trend is evident (Fig. 4).

DISCUSSION

In this study we raised the question whether physical exercise test alone beside accurate diagnosis of obstructive lesions provides an opportunity to prognose cardiovascular risk. We claim that this is possible, which is demonstrated in our study by a significant number of patients with silent ischemia. The potential gain from reducing the risk of reverse cardiac events is actually greatest in those with silent ischemia at the time of follow-up presentation, because

Table 1

MEAN VALUES OF ANALYSED PARAMETERS DURING EXERCISE TEST FOLLOW-UPS

Exercise test data/ Follow-up visit	1–3 months	3–6 months	6–12 months	12–24 months	24 months
Maximal pulse under exercise ± SD	118 ± 16	122 ± 17	121 ± 16	119 ± 15	119 ± 15
Maximal systolic blood pressure under exercise, mmHg ± SD	180 ± 31	181 ± 29	182 ± 29	183 ± 31	184 ± 32
RI (maximal pulse x maximal systolic blood pressure)/100 ± SD	213.27 ± 51.02	220.93 ± 52.55	221.55 ± 45.59	217.84 ± 47.68	219.32 ± 48.46

Table 2

ROBINSON INDEX AT DIFFERENT FOLLOW-UP VISITS FOR PATIENTS WITH RESTENOSIS

	RI at 1–3 months	RI at 3–6 months	RI at 6–12 months
Mean	226.19	209.80	211.96
Median	226.19	179.00	227.50
Std. deviation	60.01	59.58	44.26
Minimum	183.75	141.10	146.00
Maximum	268.62	297.44	256.51

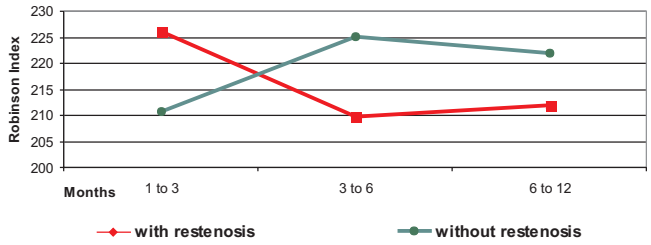

Fig. 4. Robinson Index at different follow-up visits for patients with and without restenosis.

Table 3

ROBINSON INDEX AT DIFFERENT FOLLOW-UP VISITS FOR PATIENTS WITHOUT RESTENOSIS

	RI at 1–3 months	RI at 3–6 months	RI at 6–12 months
Mean	210.79	225.03	222.00
Median	218.85	234.08	220.02
Std. deviation	52.90	46.41	47.44
Minimum	110.20	114.40	105.91
Maximum	318.20	299.52	308.14

those patients are at especially high risk (Pepine and Deedwania, 1994). Nowadays it is clear that chest pain in history does not correlate tightly with ischemic ST-segment deviation following physical loading and with haemodynamically significant stenosis on angiography either.

Published data as well as national and international guidelines state that physical exercise test following PCI is a useful method in diagnosis of restenosis in high risk or symptomatic patients and should be conducted six months after intervention (Gibbons *et al*., 2002). Our results showed that the exercise test should be done not later than three to six months after intervention. The highest rate of restenosis was observed in 50% of patients after interventional treatment of LM disease and in 45.8% for other lesion localisations calculated from all documented cases of restenosis. The importance of the physical test does not decrease later; 37.5% of all documented restenosis were registered at six months after intervention (including 50% of patients with newly diagnosed stenosis on angiography). One year after PCI the specific weight of restenosis was 16.7% of all diagnosed restenosis.

The clinical value of exercise electrocardiograms following interventional therapy in the early period is high in evaluation of early post-interventional results (Roffi *et al*., 2003). This is supported with our results, which demonstrated specificity of 100% of exercise test performed in the first six months after PCI. Exercise electrocardiograms 1–3 months after PCI did not show a shift of the ST-segment for all patients without restenosis. However, ECG of the ST-segment was registered on exercise ECG only for patients with restenosis. This demonstrates a clear correlation between ST-segment depression and restenosis. Generally, shift of the ST-segment following physical loading was documented in 60% of patients with restenosis on angiography while in 90.5% of patients with normal exercise electrocardiograms restenosis in coronary vessels was not found.

Adequate implementation of drug therapies depending on patient clinical and functional status allow to reach goals set by national and international guidelines. Based on epidemiological studies, even small decreases in low density lipoprotein cholesterol and blood pressure levels translate into significant reductions in cardiovascular morbidity and mortality (LaRosa *et al*., 2005). Moreover, especially important is the patient compliance, which can be achieved through frequently scheduled visits.

The clinical course and prognosis of patients with CHD can be modified favourably by successful translation of recommendations for secondary coronary prevention into effective clinical care. Crucial to the outcome of any preventive strategy is patient attitude to lifestyle modification and compliance with drug therapies over the long term. We tend to claim that an aggressive follow-up programme could help us to reach the goals in secondary prevention of CHD set by European Societies and Latvian Society of Cardiology.

The physical exercise test is a safe method with high specificity but is limited by poor test sensitivity for the evaluation of efficacy of interventional and drug treatment for patients with CHD. A focussed exercise test given on a regular basis indirectly influences clinical results and prognosis. Timely set diagnosis of restenosis provide necessary treatment measures, therefore, alienating reverse cardiac events such as unstable angina and myocardial infarction. Moreover, an exercise test performed on a regular basis provides essential corrections in drug therapy. After comparison of

drug therapies recommended three months and one year after PCI, we can conclude that regular follow-ups provide the opportunity to sustain acceptable patient compliance and use of medications even twelve months after an intervention.

A focussed follow-up programme with an exercise test allows to evaluate clinical status of patients as well as to determine timely possible risk of restenosis, to adapt medication doses, to reduce risk factors and to influence positively patient compliance. The exercise test provides accurate estimation of possible restenosis in patients with complete revascularisation. In patients with incomplete revascularisation the exercise test specificity is reduced. Taking into account the results of the current study, we are sure that focussed physical exercise test should be advised for all patients after interventional treatment. It is of high importance to achieve submaximal heart rate during the exercise test. In all cases when this is not possible for any reason, myocardial perfusion scintigraphy is indicated.

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MĒRĶTIECĪGAS SLODZES TESTA APSEKOŠANAS PROGRAMMAS NOZĪME KORONĀRĀS SIRDS SLIMĪBAS PACIENTIEM, ĀRSTĒTIEM AR PERKUTĀNU KORONĀRU INTERVENCI

Koronāro sirds slimību (KSS) ārstēšanas pamatā ir koronāro asinsvadu lūmena atjaunošana, ko veic ar invazīvu metodi – perkutānu koronāru intervenci (PKI), kombinējot to ar medikamentozu terapiju. Lai optimizētu šādu pacientu aprūpi un ārstēšanu, Latvijas Kardioloģijas centrā tika izveidota plānota pacientu apsekošanas programma, kuras galvenais izmeklējums ir slodzes tests. Latvijā līdz šim nav veikts šāds pētījums, kas sniegtu plašas iespējas analizēt pacientu funkcionālo stāvokli, lietotās ārstēšanas efektivitāti, iespējamo risku un prognozi pēc invazīvas KSS ārstēšanas. Izveidots PKI pacientu datu reģistrs. Slodzes tests joprojām ir KSS diagnostikas pamatmetode. Tāpat šo metodi lieto, lai noteiktu iespējamu restenozi koronārajās artērijās – procesu, kas ir patofizioloģiski atšķirīgs no primāra aterosklerozes mehānisma (atpakaļsaraušanās, vēlīna remodelācija, tromboze, neointīmas proliferācija). Mērķtiecīgi apsekoti 7300 pacienti ar KSS, kas ārstēti ar PKI (laikā no 2006. līdz 2008. gadam), izdarot slodzes testu. Apsekošana veikta 1–3, 3–6, 6–12 mēnešus pēc koronāras intervences. Veikta lietoto medikamentu grupu analīze. Atsevišķi apskatīti īpaši augsta riska pacienti ar kreisās koronārās artērijas stumbra (*LM*) stenozi. Analizēts pacientu klīniskais un funkcionālais stāvoklis, prognozēta restenozes iespējamība, koriģēti medikamenti, plānoti nepieciešamie izmeklējumi un izmaiņas ārstēšanas plānā. Pēc indikācijām veikta kontroles angiogrāfija. Apsekoto KSS pacientu grupā 17% pacientiem ir koronāras sūdzības, 13% konstatētas nozīmīgas ST segmenta izmaiņas elektrokardiogrammā slodzes testa laikā, 6,4% no šiem pacientiem angiogrāfiski noteikta restenoze koronārajos asinsvados. Gandrīz pusei šo pacientu (46% gadījumu) restenozi konstatē agrīnā periodā (3–6 mēn. pēc PKI). Atrasta pacientu grupa ar pozitīvu slodzes testu, bet bez sūdzībām („klusā išēmija") – 22% pacientu, no kuriem 41% konstatē restenozi (t.i., 9% no kopējā pacientu skaita). Arī *LM* pacientiem 50% restenožu gadījumus konstatē agrīnā periodā (3–6 mēnešus pēc PKI), pārējos 43% – 6–12 mēn. un 7% 12–24 mēn. pēc PKI. Agrīno restenožu pacientiem angiogrāfiskie rezultāti korelē ar ST segmenta išēmiskām izmaiņām EKG slodzes testa laikā, kā arī reģistrēts zemāks Robinsona indekss. Mērķtiecīga apsekošanas programma, veicot slodzes testu, ļauj novērtēt pacientu klīnisko stāvokli, savlaicīgi noteikt iespējamo restenozes risku, precīzi dozēt nepieciešamos medikamentus atkarībā no pacienta funkcionālā stāvokļa, koriģēt riska faktorus, kas varētu nelabvēlīgi ietekmēt slimības gaitu, kā arī nodrošināt augstu pacientu līdzestību.