CHANGES IN THE TREATMENT OF ISCHAEMIC HEART DISEASE

Summary of PhD Thesis

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Introduction

Coronary artery diseases and mortality are a major health problem in the industrialised western countries and that is true for Hungary as well. Myocardial infarction has become more frequent mainly in developed countries over the past decades.

Besides the modern pharmacological treatment interventional procedures (percutaneous transluminal coronary angioplasty (PTCA), percutaneous coronary intervention (PCI), stenting, intraaortic ballon pump, resyncronising therapy, implantable cardioverter–defibrillator) the quality of life of the patients and the mortality data were improved.

We would like to demonstrate the development, the present status and perspectives of interventional cardiology in Zala County Hospital, Zalaegerszeg.

Aims of the investigations

In our investigations we aimed to find the answer to the following questions:

1. The aim of our first study was to examine myocardial perfusion changes with the use of internal mammary artery graft in patients who underwent cardiac surgery.
2. The aim of our second study was to examine if the treatment of acute ST-segment elevation myocardial infarction (STEMI) patients by primary PCI changes mortality rate in STEMI patients.
3. The aim of our third study was to examine the efficacy of drug-eluting stents for ischaemic heart disease.

I. Prospective evaluation of thallium-201 reinjection in single-vessel coronary patients undergoing coronary bypass surgery

Introduction:

A possibility for enhancement of the sensitivity of thallium-201 (^{201}Tl) myocardial perfusion scintigraphy in the detection of injured but viable myocardium is the reinjection of a half dose of ^{201}Tl immediately after the resting study. This method offers better counting statistics than 24-to 72-h delayed imaging, furthermore, the investigation can be completed within 1 day, which is more practicable for the patient.

It is of special interest to establish whether this modified technique of myocardial perfusion scintigraphy is suitable for the identification of reversible injured myocardium before revascularization surgery and for the prediction of the recovery of nutritive perfusion.

Aims:

We have investigated the predictive value of ^{201}Tl reinjection in a homogeneous patient group with single-vessel coronary disease.

The aim of the study was to clarify whether ^{201}Tl reinjection method is suitable for the prediction of myocardial perfusion soon after successful coronary bypass grafting.

Patients and methods:

These studies were carried out at the University of Szeged Faculty of Medicine (collaboration with Department of Nuclear Medicine, Department of Cardiac Surgery and 2nd Medical Clinic, Albert Szent-Györgyi Medical University).

Twenty-two patients (5 females, 17 males, mean age 51.9 ± 9.8 years, range 39-69 years) with single-vessel left anterior descending (LAD) coronary artery disease were investigated before and after coronary bypass surgery. Five patients had anamnestic non-Q and two patients Q-wave anterior myocardial infarction.

Coronary angiography documented LAD coronary occlusion in five patients, and subtotal LAD lesions in 17 patients. The other main coronary vessels were without significant narrowing.

During coronary bypass surgery the internal mammary artery was used for revascularization of the LAD territory. None of the patients had documented perioperative myocardial infarction.

Investigation of myocardial perfusion. Dipyridamole stress myocardial perfusion scintigraphy was performed, using single-photon emission computed tomography (SPECT), in each patient 4-10 days before and 14-25 days after bypass surgery.

^{2Ol}Tl reinjection. Before bypass surgery and after completion of the redistribution study, 1 mCi of ^{2Ol}Tl was injected. Repeated SPECT was performed 10 min and 1 h following reinjection. No reinjection was performed after surgery.

Results:

Left ventricular function

Ventricular hypokinesia was proven by radionuclide ventriculography before surgery in 18 patients. On radionuclide ventriculography, the left ventricular ejection fraction lay in the range 33%-62% (mean 50.8% ± 8.2%).

After surgery, the left ventricular wall motion was normalized in seven patients, and improved in one patient. The postoperative left ventricular ejection fraction lay in the range 45%-74% (mean 56.2% ± 10.1%).

Dipyridamole test

Before surgery, the complete dose of dipyridamole was administered in 19 of 22 patients. Dipyridamole infusion was interrupted after 3.5 instead of 4 min in three patients, due to severe chest pain in the 3rd minute of the stress.

Aminophylline was necessary in 13 patients; five of them received additional anti-anginal meditation (nitro-glycerine and/or nifedipine).

After surgery, the whole dose of dipyridamole was administered to all patients. No aminophylline or other drugs were given after stress.

Haemodynamic data and electrocardiographic (ECG) changes during stress

Before surgery, significant ischaemic. ECG changes were present in 4 of 22 patients; after surgery, no significant ECG changes were noted during stress. Before surgery, 14 patients had chest pain during stress (in 13 of them aminophylline was given); after surgery, one patient had an atypical feeling of chest discomfort at the end of stress.

Myocardial perfusion during stress before surgery

A significant perfusion defect was seen on the preoperative stress scintigrams in 21 of 22 cases. The defect scores ranged from O to 28, with a mean of 17.0.

In one patient, with 99% proximal LAD narrowing, the stress scintigram was normal. In this patient the dipyridamole infusion was interrupted after 3.5 min because of typical chest pain and a 2-mm descending ST depression on the ECG. The patient received 240 mg aminophylline, nifedipine and sublingual nitroglycerine.

Three-hour resting perfusion before surgery

The 3-h resting images revealed a significant redistribution in 19 of 21 patients with stress perfusion defects, but none of them exhibited completely normal resting images. The score difference between the stress and 3-h resting studies ranged from 1 to 17, with a mean of 6.9.

The two patients without significant redistribution had subtotal coronary lesions and were without anamnestic myocardial infarction. Dipyridamole infusion was completed in both patients. No medication was necessary in these cases.

The patient who had normal stress myocardial perfusion exhibited a significant paradox redistribution of the apical myocardial area on the 3-h resting image.

Changes in ^{2Ol}Tl distribution soon after reinjection

Further decreases in defect severity and/or defect size were observed on the 10-min post-reinjection images in 14 of 22 patients with perfusion defects on the 3-h redistribution images. The decrease in score ranged from -3 (paradox redistribution) to 10, with a mean of 3.0.

The 10-min post-reinjection images exhibited completely normal myocardial perfusion in 4 of 22 patients. The images acquired t h after reinjection differed significantly from the 10-min post-reinjection images in 7 of 22 patients. In four cases significant filling of perfusion defects was observed, while in three patients a paradox redistribution was noted.

Perfusion after bypass surgery

After bypass surgery, normal perfusion was found in 14 of 22 patients on both the stress and the 3-h rest images. A significant, but minimal redistribution was noted in four cases, and a paradox redistribution in two.

A significant decrease in the mean defect score from 10.1 to 7.1 was observed after reinjection, and a further decrease from 6.4 to 3.1 after bypass surgery.

Stress images after bypass corresponded to the stress images before bypass in three cases, to the 3-h redistribution images in two cases, to the 10-min post-reinjection images in seven cases and to the 60-min post-reinjection images in 11 cases. Resting images after bypass corresponded to the stress image before bypass in three cases, to the 3-h redistribution images in two cases, to the 10-min post-reinjection images in seven cases and to the 60-min post-reinjection images in ten cases.

The 60-min post-reinjection image before surgery appears to be the best predictor of myocardial perfusion after bypass.

Conclusion:

We performed dipyridamole stress testing before and after surgery, which is a safe alternative to ergometric stress testing with similar diagnostic efficacy.

Our patient group consisted only of single-vessel LAD patients, which results in a well-definied area at risk that can be investigated relatively free of possible imaging artefacts, e.g. due to diaphragmatic absorption. We observed a reduction in defect severity of 30% following reinjection.

We generated two sets of reinjection images. The first was acquired, as prosposed by others, immediately after reinjection, and the second, 1 h later. The reason for acquisition of the second post-reinjection images was the assumption that redistribution of ^{201}Tl may also occur after the second injection in patients with severe resting hypoperfusion. As regards the predictive value of preoperative scintigrams, the images obtained 1 h after reinjection were found to correlate most closely with postoperative study.

Our then investigations at the Szeged University of Sciences proved that post-reinjection ^{201}Tl images before surgery are good predictors of myocardial perfusion after revascularization. The best results are obtained if imaging is performed 1 h after reinjection.

II. Changes in the mortality of acute myocardial infarction in the area of Zalaegerszeg. Effects of the first 24 hour ST-elevation acute myocardial infarction intervention service in Hungary.

Introduction:

Invasive cardiology, i.e. primary PCI is already a basic requirement of up-to-date medical care of acute myocardial infarction nowadays. However, American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines of 1999 positioned PCI as a Class I recommendation only as an alternative of thrombolysis and for the treatment of patients with a complicating cardiogenic shock. First, we organized a 24 hour intervention service for acute myocardial infarction at the Department of Cardiology in the Hospital of Zala County, Zalaegerszeg, Hungary in 1998.

Aims:

We wished to examine the effect of the Cardiology Centre at Zalaegerszeg, established in 1994, and in particular of its Haemodinamics Laboratory on mortality data of the region. The first interventions in acute myocardial infarction were performed in 1996. Our study covers the period between 1997 and 2004.

Patients and Methods:

The Western Transdanubian Regional Institute of the Hungarian National Public Health and Medical Officer Service processed the mortality data of the period between 1997 and 2005 in the Western Transdanubian Region and in the area of Zalaegerszeg, and compared those with each other and with the national average published by the Hungarian Central Statistical Office. With the help of our own computerised data base, we studied the changes in the number of invasive interventions during this period, and correlated them with mortality statistics. We studied the Hungarian national, West-Transdanubian, and Zalaegerszeg areal mortality data in relation to hypertension, stroke, malignancies and myocardial infarction.

For studying the changes of mortality rate in time, we calculated standardised mortality rate (SMR); in order to avoid potential bias due to the small number of cases, we smoothed the data with moving averaging of 3 years' time span. For calculating the indices, we used the age distribution of "European Standard Population" of 1976 as reference. Analysis of mortality conditions in the area was performed on the base of mortality data in the period

between 1996 and 2005. For the analysis of mortality situation, national and areal numbers of mortality of the age groups were provided for us by the National Institute of Environmental Health based on the data of the Hungarian Central Statistical Office. European data of mortality were collected from the "European Heath for All Database" of the WHO. We note here that our statements concerning the European Union (EU) reflect a situation before May 2004, i.e. EU of 15 member states, as our study also covers this period.

For testing the study hypothesis, we used a statistical test, the Z test, as p value determined from its result serves as a base for assessing the level of significance. No level of significance was determined for areas where the actual number of death cases was <5.

Results:

There were no detectable differences in mortality rates between nationwide Hungarian and regional statistics, but as compared to the average of the EU, we found approximately twofold and 1½ fold values in male and female patients respectively. Cardiovascular diseases are responsible for approximately a half and 3/5 of mortality in men and women respectively. Analysis of mortality due to coronary disease showed no differences within the same gender but the risk of male patients was 5 times higher in comparison to female patients in the three regions studied. We found early coronary mortality in men of the Zalaegerszeg area (population between 45 and 65 years) initially higher as compared to the national and Western Transdanubian average, while there was no difference in women. However, in the age group of >65 years a significant difference can be observed also in women. During the studied period, the mortality of patients in the Zalaegerszeg area has visibly and significantly decreased both in men and in > 65 year-old women, while national and Western Transdanubian values show stagnation. Although it did not constitute a subject of our study, mortality rates in other areas of the Western Transdanubian region might show an increase that was compensated by the improvement in the Zalaegerszeg data.

The effect on mortality rates exerted by the Haemodinamics Laboratory can be illustrated primarily by the change in the data of early mortality due to myocardial infarction. The improvement of our mortality statistics is not due to some change in the prevalence of myocardial infarction, in 2005 such data of ours correlated with the national average.

In the male population belonging to the laboratory's attraction zone, mortality rates decreased to a higher extent in both studied age groups in comparison to the national and Western Transdanubian average. While the extent of decrease was 48% (>65-year-old population) and 51% (45 to 64-year-old population) of the area in the last studied period in comparison to the

baseline, the Hungarian national and the regional averages only approached 30%. As a result of the favourable process, the +15% relative risk of men above national average at the beginning of the period reached a mortality risk which was lower by 17% at the period's end. Also in women the decrease is marked more in the younger age group (45 to 64-year-old population: 56%; >65-year-old population: 38%), although this is less spectacular because of the relatively low mortality rate seen in the younger age group. Unfortunately, the change in the mortality rate of acute myocardial infarction was not associated with any decrease of other vascular mortality. While national and Western Transdanubian data show a decreasing trend in relation to hypertension and cerebrovascular disease, a stagnation can be seen in the Zalaegerszeg area, and even a significant increase occurred in the >65-year-old population.

Conclusion:

Hungarian statistics of mortality and morbidity have been led by cardiovascular diseases. Acute myocardial infarction constitutes the most frequent acutely developing form of cardiovascular diseases. Based on European statistics, Hungary belongs to countries with high cardiovascular risk; the mortality due to myocardial infarction significantly exceeds the average of developed countries. At the beginning of the 1990s, the cardiovascular mortality as well as the early mortality due to myocardial infarction in the Zalaegerszeg area exceeded both Western Transdanubian regional and Hungarian national averages. Based also on these dismal statistical data, the Cardiology Centre that possesses units of invasive cardiology and cardiac surgery as well was brought into being in 1994. Preceding even the European and North American recommendations, we developed a 24 hour emergency service for patients with (initially only) acute STEMI which soon extended to all kinds of acute coronary syndrome. Analyses performed yearly on the base of our own data (which demonstrated a reduction of the mortality rate in the hospital phase of STEMI) confirmed our belief that we were on the right track. Based on numerous studies published in the meantime, primary PCI for STEMI has already become a Class I/A recommendation at present.

The acute 24 hour intervention care for acute myocardial infarction, launched as the first of its kind in Hungary, has improved mortality statistics of the area to a significant extent in comparison to the national average. Initially we performed primary intervention only in "selected" patients (who were young and presented themselves with a short pre-hospital interval), but at the sight of the excellent results we included an increasingly wider scope of patients into the acute care. At the beginning of the period, hospitals belonging to our region of care used lysis therapy in their patients, according to the recommendations of that time.

The differences in mortality rate, particularly in 2000 to 2001, can also be considered as differences between lysis and primary PCI. It should be underlined that, although further invasive centres began functioning in the region and 16 centres provide STEMI service nationwide, the results of the experienced team which has gained great routine, represent an advantage for patients in the Zalaegerszeg area up to now. Based on our data, we can state, that a significant reduction of mortality rate can be attained by primary PCI therapy of STEMI, the material and technical conditions of which have been realised, so that further development of the system at striving for perfection is justified. We have to seek, in addition to prevention, early recognition of the disease and – as early as possible – transport of patients, preferably directly, onto the table for catheterisation.

III. Experience with Endeavor stent implantations

Introduction:

The high risk acute coronary syndrome (ACS) (with ST segment elevation, non-ST segment elevation, troponin positive - NSTEMI) should be treated with PCI, which could be balloon angioplasty (PTCA) with or without stent implantation, or primary stent implantation. In case of PTCA re-narrowing of coronaries occurs in 30-40% of all cases in 3-18 months after the procedure. The phenomenon is called restenosis. This is the most common disadvantage of PTCA. The incidence of restenosis can be lowered with the use of stents (the first coronary stent in a human was implanted by Sigwart et al. in 1987 to 15-30%, but it can’t be eliminated. The restenosist after the use of stents is called in-stent restenosis (ISR).

To avoid the ISR drug eluting stents (DES) were developed and used, which do not allow the neointima formation, thus ISR is very rare, indeed, but the occurrence of stent-thrombosis is higher than in cases of bare metal stents (BMS).

The Endeavor is a new DES based on chrome-cobalt stent (Driver) covered in antiproliferative phosphorylcholin polymer ABT – 578 (a zotarolimus, rapamycin-like material). The development of this DES was ruled by the fact that the neointima proliferation, in however small measures, is occurring, so the frequency of stent-thrombosis can be reduced.

Aims:

In a prospective study our aim was to follow up our patients regarding to the incidence of in-stent restenosis, stent thrombosis and clinical end points (the need of new coronary angiography, revascularization) after Endeavor stent implantation. Our results have been compared to the data found in the Medline database.

Patients and methods:

Endeavor stents have been implanted in patients undergoing elective or acute coronary angiography in Cathlab of the Zala County Hospital with the following indications: Complex B and C type lesions susceptible to restenosis and after recanalization of chronic total occlusions (CTO).

Detailed database has been created in which the indication and the locus of stent implantation, the medical history and concomitant medications have been stated.

Patients were followed-up with treadmill stress test according to Bruce protocol 1, 3, 6 and 12 months after the procedure and via telephone consultations, respectively.

All patients gave their written consent.

Data were processed and statistical measurements were made using Excel software.

Results:

Endeavor DES implantations were successfully performed in 99 patients (65 male (65.6%), 34 female (33.7%), average age 62 ± 12 years) between October 2005 and September 2006. The diagnostic coronary angiography proved multi coronary disease in 59 patients (59.6%). 90 patients were treated with 1 stent, 2 stents were implanted in 6 patients, while 3 patients received 3 Endeavor stents.

Endeavor stent implantation has been successful in 98% of cases, 2 stents could not be implanted because of technical difficulties. Besides Endeavor other types of stents were used in 40 patients (41.4%) (3 DES, 37 BMS). Multi vessel PTCA was performed in 20 cases, in another 20 patients Endeavor and another stent have been implanted in the same coronary artery. In the aggregate 166 stents were implanted in 99 patients (1.67 stents/patients). The average Endeavor stent length was 23.16 mm, the average stent diameter was 2.98 mm. The localization of the implanted stents was as follows: Left anterior descending artery (LAD) 61 (25 proximally), circumflexus (CX) 11, right coronary artery (RCA) 21 (4 into the orifice), left main (LM) 3, grafts (saphena - SVG or left internal mammary artery - LIMA) 3. 29 stents

were implanted in bifurcational lesions (LAD-diagonal, dominant obtuse marginal - CX-OM), recanalization of CTO with Endeavor stent has been performed in one case.

All patients were treated with the combination of 100 mg acetylsalicylic acid (ASA) and 75 mg clopidogrel for 12 months. The combination therapy of glycoprotein (GP) IIb/IIIa receptor blockers and intravenous Na-heparin was used in 14 patients for 12 hours following PCI. During the follow-up period planned or unplanned coronary angiography was performed in 36 patients (36.4 %). Target vessel revascularization was necessary in 13 patients (13,1%) (6 coronary artery bypass graft - CABG, 7 rePTCA), 11 patients had 3 vessel disease, 9 had LAD-diagonal bifurcational lesions, 1 SVG, 1 LM and 2 RCA. Five of 13 suffered from diabetes. All stents except the ones implanted in the LM were longer than 18 mm (diameter ranged from 2.75 to 3.5 mm). Significant restenosis was observed in 8 patients (8.1%). Subacute stent-thrombosis (within 10 days) occurred in 2 patients (2.0%). There wasn't any late stent-thrombosis.

Five patients died during the follow-up period: 2 patients due to the progression of heart failure (no restenosis), 1 patient after a huge stroke and 1 patient chilled during an alcohol abuse state. NSTEMI with cardiogenic shock due to restenosis caused the death of 1 patient.

Conclusions:

PTCA re-narrowing of coronaries occurs in 30-40% of all cases in 3-18 months following the procedure. The incidence of restenosis can be lowered with the use of stents to 15-30%. The restenosis after the use of stents is mostly due to neointima formation.

To avoid ISR, drug eluting stents are used, which block neointima formation. ISR is very rare but the incidence of stent-thrombosis exceeds those in BMSs.

The Endeavor drug eluting stent is based on a chrome-cobalt Driver stent covered in antiproliferative phosphorylcholin polymer ABT – 578. It is a rapamycin-like material, which bonds $FKBP_{12}$ protein. This complex prevents the mTOR signal transmission and as a result it blocks cell cycle and tissue proliferation. Efficacy and safety were studied in ENDEAVOR I-III. clinical trials. The 100 patients elected for Endeavor I trial had de novo, A-B2 type coronary stenosis, and the implanted Endeavor stents were shorter than 18 mm. Target lesion revascularization (TLR) and target vessel failure (TVF) was 2% after 4 and 12 months and remained constant after the 24 month follow-ups. In-stent late loss was 0.61 mm, in-stent binary restenosis was 5.4%. Subacut stent-thrombosis (< 10 days) occurred in one patient only, and there weren't any late stent-thrombosis after the 24 month follow-ups, either. After 24 months the incidence of major acute cardiac event (MACE) was 3%. These data are

important in the light of several studies reporting the high incidence of late stent-thrombosis after DES implantation causing higher mortality compared to BMS in 2006 and 2007. However these findings referred to the first generation of DESs, in case of second generation Endeavor stent these late effects could not be proven.

Our registry affirmed the results of the ENDEAVOR I. trial in a population with more severe and longer coronary stenosis. We showed that these stents are well useable (with only a 2% rate of failure), there wasn't any difference in the incidence of stent-thrombosis compared to earlier results, and we could not detect late thrombosis. The prevalence of in-stent restenosis was higher compared to the ENDEAVOR I. trial, but the difference can be explained with the more complex and longer lesions in our population. Summarizing we can conclude that the ENDEAVOR stent is suitable for implantation in complex, longer coronary lesions. Our long term follow-up data doesn't prove those opinions which prefer BMS implantation in all patients referring to the late adverse events of the drug eluting stents.

New observation

The following conclusions can be drawn from our investigations:

1. The post-reinjection ^{201}Tl images before surgery are good predictors of myocardial perfusion after revascularization. The best results are obtained if imaging is performed 1 hour after reinjection.
2. Introduced the first 24-hour duty in Hungary to provide primery PCI care for STEMI patients.
3. The acute 24 hour intervention care for acute myocardial infarction has improved mortality statistics of the area to a significant extent in comparison to national and regional average.
4. The extension of STEMI invasive care to the elderly shows good results similar to those in younger age groups.
5. We have created an Endeavor registry involving “real world” patients.
6. Our Endeavor-registry affirmed the results of the ENDEAVOR I. trial in a population with more severe and longer coronary stenosis.
7. The professional team, which I am the head of, first proved that the ENDEAVOR stent is suitable for implantation in complex, longer coronary lesions.
8. Our long term follow-up data don’t prove those opinions which prefer bare metal stent implantation in all patients because of the late adverse events of the drug eluting stents.

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