

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

**FACTORS AFFECTING THE RESULTS OF ACUTE
PERCUTANEOUS AND ELECTIVE SURGICAL
REVASCULARIZATION IN CORONARY ARTERY
DISEASE**

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**UNIVERSITY OF DEBRECEN
Kálmán Laki Doctoral School**

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Head of the **Examination Committee:** Prof. György Balla MD, PhD, DSc,
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Members of the Examination Committee: István Lőrincz MD, PhD
Attila Mohácsi MD, PhD

The Examination takes place at the Szontagh library of Department of
Pediatrics, Faculty of Medicine, University of Debrecen
at 11:00 a.m., on 26th September, 2017.

Head of the **Defense Committee:** Prof. György Balla MD, PhD, DSc
Reviewers: Prof. Pál Soltész MD, PhD, DSc
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Members of the Defense Committee: István Lőrincz MD, PhD
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The PhD Defense takes place at the Lecture Hall of Augustza Building,
Faculty of Medicine, University of Debrecen
at 13:00 p.m., on 26th September, 2017.

INTRODUCTION

Cardiovascular diseases are among the leading causes of death worldwide. In Hungary, cardiovascular diseases, including ischemic heart disease and its complications, account for more than half of all mortalities.

Imbalance between oxygen demand and supply results in poor myocardial circulation and subsequent ischemia. Ischemic heart disease (IHD) is caused by the narrowing or occlusion of coronary vessels, which leads to the damage and, eventually, necrosis of the myocardium. Remodeling of the connective tissue in necrotic myocardial areas can be observed. This is accompanied by the dilation of cardiac chambers, decrease in the pumping function of the left ventricle and, in the end, cardiac failure. Overall, these events are to blame for the steady decline in a patient's condition leading to a gradual decrease in their quality of life. Life expectancy can be improved through early revascularization such as percutaneous coronary intervention (PCI) or even an elective coronary artery bypass graft (CABG) surgery. Mortality from acute myocardial infarction has decreased all over the world due to the beneficial effects of such interventions.

Ischemic heart disease can be traced back to atherosclerosis, which is characterized by a progressive degenerative process in certain layers of the vascular wall. The damaged area in the vascular endothelium is covered by a core rich in lipoproteins and cell debris, and a fibrotic 'cap' surrounding the core. Over time, this lesion becomes calcified and a plaque is formed. In addition, chronic inflammation, caused by various inflammatory cells (macrophages, and T and B lymphocytes) as well as cytokine cascades, takes place in the plaque. Unstable plaques are prone to rupture culminating in acute coronary syndrome. Stable plaques, however, can cause ischemia by reducing the lumen of the coronary vessels and manifest themselves in the form of stable angina. Stenosis of a coronary vessel exceeding 50% of its diameter

can significantly reduce blood flow and it may be indicative of revascularization, i.e. terminating hypoperfusion to areas with deficient blood supply. In addition to the narrowing of coronary arteries to just 50-70% of their normal diameter, instability factors of the plaque (edema, triggering vasospasms, thrombocyte activation) also play a decisive role in the development of coronary events.

Based on the ECG, two types of acute myocardial infarction are distinguished: ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI). STEMI is most commonly caused by the presence of an obstructive thrombus in coronary arteries resulting from the rupture of a soft, cholesterol-filled plaque. Acute infarction is usually accompanied with typical chest pain, although it may produce atypical symptoms due to changes in pain sensation if certain comorbidities such as diabetes or subsequent neuropathy are present. Changes in the ECG pattern in silent myocardial infarction (MI) or MI with atypical symptoms can be attributed to ischemia only in cases confirmed by coronary angiography. Based on experiments, necrosis spreads laterally along the endocardium for approx. 40 minutes, and after that it spreads transmurally, in accordance with the 'wave front principle'. Following induced coronary occlusion, however, disturbed heart wall motion develops in ten minutes and will not significantly change in the next six hours. It is the period of time between the beginning of an acute event and revascularization (ischemic time) that plays a very important role in the course of the disease. Myocardial damage can be reduced by restoring circulation along the blocked epicardial artery as soon as possible, but the longer the delay doing so the greater the likelihood of permanent myocardial dysfunction and cell death.

Making the diagnosis of STEMI, a cardiologist can rely on ECG results supported by those of echocardiography revealing regional changes in wall motion.

Furthermore, information about left ventricular function is also of great importance. Primary coronary intervention performed in STEMI can improve left ventricular function and prevent remodeling and subsequent dilation after an infarction. However, little data is available about the exact relationship between ischemic time and the extent of disturbed heart wall motion and the size of irreversible myocardial necrosis.

In addition to the duration of ischemia, the presence or absence of a preconditioned state of the myocardium and the type of an evolving functional loss are also of importance. Short-time severe ischemia can cause lasting but reversible functional disturbance, a condition also known as ‘stunned myocardium’. Myocardial contractility gradually returns to normal in cases like this. In contrast, chronic ischemia can cause permanent loss of myocardial functions, therefore partial or complete reversibility of myocardial functions can only be achieved after percutaneous or surgical revascularization of the hibernated myocardium.

Role of echocardiography in assessing the systolic function and regional disturbance of heart wall motion

Echocardiography, allowing both qualitative and quantitative measurements of left ventricular systolic function, serves as a basic examination technique in evaluating heart function. Measuring the ejection fraction (EF) of the left ventricle has been used widely due to easy performance and its predictive value. Techniques known as Simpson’s biplane method or modified Simpson’s rule as well as the area-long-axis measurement have been commonly used to accurately measure global left ventricular function; they are also recommended for research purposes.

Disturbed motion in certain areas of the left ventricle and changes in the thickness of ventricular walls are clearly visible. These disturbances and changes

develop as a result of myocardial ischemia triggered by the narrowing of coronary vessels. In addition to assessing global left ventricular systolic function, it is also highly important to visualize regional or segmental wall motion disturbance using echocardiography. Based on contractility and the severity of disturbance, segmental wall motion is classified as follows: 1-normokinesis, 2-hypokinesis, 3-akinesis, 4-dyskinesis and 5-aneurysm. The American Society of Echocardiography had set up a 16-segment model which was later replaced by a new, 17-segment one. The aim of the model was to correspond areas regarding their blood supply based on echocardiography, isotope scan and coronarography tests. Calculation of the wall motion score index is based on the severity of the condition and the contractility of the individual segments. Wall motion score index (WMSI) is obtained by adding up the scores of wall motions and dividing the sum by the number of the segments examined. WMSI informs about the severity and size of disturbance in regional wall motion, the normal value being 1.

Importance of percutaneous coronary intervention

In addition to revealing the anatomy of coronary vessels, emergency percutaneous coronary intervention performed during acute myocardial infarction enables the physician to find out about the coronary arteries' structural or functional changes, and assess the extent of coronary stenosis. Opening up the lesion causing ischemia and recanalization allow reperfusion in the vessel in a short time. The ischemic effect of coronary stenosis is influenced by the decrease in flow reserve capacity. There is certain correlation between coronary reserve and the percent stenosis as well as residual lumen diameter (mm). Although quantitative coronary angiography (QCA) provides much more reliable and more easily reproducible

results, the visual assessment of percent stenosis has become more popular in clinical practice. The functional importance of stenosis depends on several factors, e.g. the degree, number and length of stenoses, whether there are multiple stenoses, if the narrowing is symmetrical or asymmetrical; blood viscosity also plays a role. The presence or absence of a collateral vessel network, resistance in the vascular system and vasomotor tone are also of importance. Fractional flow reserve (FFR) measurements are especially helpful in establishing the severity of the hemodynamic aspects of threshold stenosis.

Importance of coronary bypass surgery

Coronary artery bypass graft (CABG) surgery, which allows complete revascularization, is the most commonly chosen treatment option in chronic ischemia involving multiple coronary stenoses. The oxygen and nutrient supply to tissues with insufficient perfusion is provided through ‘substitute’ vessels. Based on type, grafts used in CABG surgery are either arterial or venous ones. The internal mammary artery (IMA) has the longest lifetime; it can serve the patient until the end of life. In contrast, the chance for the saphenous vein to stay open is very low due to degenerative processes taking place in the body. However, type of these vessels are widely used since they are easily accessible, elastic and have a low dissection rate. The fact that the venous endothelium cannot completely adapt to higher pressure in the arterial system serves as an explanation for degenerative processes occurring but degeneration can also be triggered by perioperative injury to the venous endothelium, winding course of the vein, disproportion between the outlet of veins and entrance of arteries. At the beginning thrombotic processes but later hyperplasia of the tunica intima play a role.

There is no significant disproportion in the diameter of the graft and the coronary artery, especially if IMA grafts are used in arterial revascularization. Moreover, the structure of the grafts' tissues also contributes to their capacity to endure permanently high intraluminal pressure without damage. After the first postoperative year, it is atherosclerosis that may become the most serious degenerative process if IMA grafts are considered. Fortunately, atherosclerosis affecting IMA grafts is rare. The left internal mammary artery (LIMA) is the most commonly used bypass graft, which is attached to the left anterior descending coronary artery. The long-term rate at which LIMA-LAD grafts stay open is approximately 90%, which is quite high and predictive of a good clinical outcome.

However, the number of studies reporting LIMA graft insufficiency caused by diffuse narrowing of the graft has been on the rise lately. Earlier, publications about the longitudinal thinning of IMA grafts as well as the "distal thread phenomenon" also appeared. The condition, i.e. damage to the graft is widely known as the "string phenomenon". This most commonly occurs when a LIMA graft is stitched to a narrowed coronary artery but the narrowing is not of critical size ($\leq 50\%$). In other cases, injury and spasm of the LIMA graft is suspected which occurs during preparation and mobilization. The role of inflammation accompanying post-pericardiotomy or the so called steal phenomenon cannot be disregarded either. CABG surgery on coronary arteries with medium narrowing may lead to the development of competitive flow between the native coronary artery and the graft. This is associated with the fact that there are individual differences in coronary flow in the stenotic lesion at rest and during exertion and, also, differences are observed in the way a LIMA graft can adapt to the conditions of flow. The relationship between competitive flow and the LIMA graft staying open is also being debated.

Strategies in treating ischemic heart disease

It is possible to slow down the progression of atherosclerosis, an underlying condition of ischemic heart disease, by optimal medication and the elimination of cardiovascular risk factors such as smoking, hypertension, high blood cholesterol levels and diabetes mellitus. The initial strategy of treatment for patients having complaints but belonging to the low-risk group for cardiovascular diseases includes the use of drugs. Patients in the high-risk group, however, are recommended to undergo primary invasive treatment (percutaneous coronary intervention /stent implantation) and/or coronary artery bypass graft surgery.

As part of secondary prevention, among the options of drug treatment the following must be highlighted as basic therapy: 1. acetylsalicylic acid/clopidogrel; 2. beta- receptor blockers; 3. angiotensin-converting enzyme inhibitors (ACEI) or – in case a patient is intolerant to ACEI – angiotensin-receptor blockers; 4. statins and/or ezetimib. Second-line medication should include: 1. Ca²⁺-channel blockers (belonging to the non-dihydropyridine type); 2. If-channel inhibitor (ivabradin); 3. long-term treatment with nitrates is indicated only if the patient complains of angina symptoms as there is no evidence supporting the role of nitrates in improving survival; 4. trimetazidine to alleviate angina pain and provide cytoprotection.

AIMS

- 1) Investigation into the relationship between changes of left ventricular wall motion and the location of coronary occlusion in patients admitted to hospital for myocardial infarction with ST elevation;
- 2) Investigation into the relationship between ischemic time (length of time from the beginning of chest pain to the opening of the coronary artery) and the size and severity of left ventricular wall motion disturbance detected in the echocardiogram performed on admission to hospital;
- 3) Investigation into the relationship between ischemic time and improvement in left ventricular wall motion observed in previous investigations, following revascularization;
- 4) Evaluation of the chances how long LIMA grafts stay open after elective coronary bypass surgery in patients with chronic ischemia;
- 5) Investigation into the incidence of the string phenomenon in LIMA grafts, and, in individual cases, the role of competitive flow.

PATIENTS AND METHODS

1. Patients and methods in STEMI

Patients suffering their first STEMI and admitted to our department for primary coronary intervention (PCI) for the first time were selected in the first part of the study. Further criteria included the following: complete occlusion of a single coronary branch and no complication or adverse event in the follow-up period. Other options of selection were as follows: 1. absence of macroembolization in the distal part of the affected epicardial coronary vessel; 2. TIMI III flow after stent implantation. The exclusion criteria included: 1. angina after PCI; 2. another myocardial infarction in the next six months; 3. stenosis exceeding 50% in the non-culprit coronary vessels. Retrospective data analysis was performed.

During 12 months of selection, 57 patients met the above criteria. Among cardiovascular risk factors, obesity (calculated body mass index – BMI), smoking, hyperlipidemia, hypertension, diabetes mellitus, as well as certain comorbidities such as stroke/TIA and peripheral arterial diseases were introduced into the documentation.

Every patient underwent echocardiography on admission, prior to the intervention, and at 2.8 ± 0.2 months, postoperatively. The echocardiograms were performed using an Acuson-Sequoia echocardiograph fitted with a 3.5 MHz harmonic imaging transducer (Siemens Medical Solutions of Siemens AG, Erlangen, Germany). End-diastolic (EDD) and end-systolic (ESD) left ventricular diameters were measured in a parasternal longitudinal view. Left ventricular ejection fraction was determined using software with automatically integrated Simpson's formula after determining the left ventricular endocardial border, in apical four-chamber and two-chamber views. Changes in wall motion were recorded in the 16-segment left ventricular model.

Segmental wall motion was determined as follows: 1- normokinesis, 2-hypokinesis, 3-akinesis, 4-dyskinesis, 5-aneurysm. Dividing the score for each left ventricular segment by 16, we calculated the wall motion score index (WMSI), which equals 1 if normokinesis is detected in all of the 16 segments. Regional wall motion score index (rWMSI) was obtained similarly, with the inclusion of the affected left ventricular segments.

In order to compare results via imaging and process clinical data, we used the Holistic Coronary Care (HCC) program based on integrated 16-left-ventricular-model program, Microsoft Access 2000 (Coronart Ltd. Debrecen, Hungary), developed at the Department of Cardiology at the University of Debrecen. The program allows the registration of the details of a patient's history, laboratory parameters, dates when clinical symptoms began and details of drug therapy. In order to evaluate the results of echocardiography and coronarography we used a cardiac polar map, also known as the 'bull's eye map' and visualized all of the 16 left ventricular segments together. There are 12 (3x4) types of coronary circulation, determined on the basis of the HCC system, including the individual coronary branches - i.e. left (LAD), circumflex (CX) and right (RCA) -combined with the dominance of the coronary arteries (superb-right, right, balanced or left dominant). The software automatically shows the left ventricular segments supplied by the blocked coronary vessel. Providing the exact location and extent (%) of the stenosis, the areas at risk can be color-coded on the cardiac polar map. In order to render the results comparable, differences in wall motion, recorded in the 16 segments during echocardiography on admission to the hospital and during the follow-up period, were also displayed in the color-coded polar map. Thus the proportion of the areas at risk (based on coronary perfusion) and left ventricular segments exhibiting disturbed wall motion during echocardiography, as well as improvement in wall motion can be

compared readily. The extent of improvement could be assessed using the regional wall motion score index (rWMSI) comparing the results obtained on admission and during follow-up echocardiography.

Statistical considerations

In the first part of the study sample size calculation was performed with an assumption that a 5% change in the EF during the follow-up with a 10% SD in the average of the values can be detected with a 0.90 power of the test. 43 patients were aimed to include into the study to achieve this power with a 0.05 probability of making a Type I error. Categorical variables are reported as counts (percentages) and continuous variables as mean and standard deviation (SD). Kolmogorov-Smirnov test was performed to examine the normality of parameter distribution. All variables showed normal distribution. Results are expressed as mean (95 percent confidence interval, CI). The p-value threshold for significance used was a two-sided value of 0.05. Positive and negative predictive values were calculated by standard methods. Within-subject differences between follow-up and admission parameters were tested using Student's paired t-tests, separately in the early and late groups. Late vs early group comparisons were evaluated using Student's two-sample t- tests, separately at admission and follow-up. Regression analysis was used to determine the relation between the change in regional wall motion and the elapsed time from the symptoms. All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics v20.0.0), USA.

2. Patients and methods in chronic ischemia

In the second part of the study, we examined the causes of competitive flow in the background of IMA graft insufficiency. Diffuse graft narrowing (string sign) developed in 6 (6%) out of the 105 patients selected for the study. All of them received LIMA grafts stitched to their LADs, individually or in a sequence, on the diagonal branch; further 1-3 distal saphenous vein grafts or radial artery anastomoses were inserted, which meant an average of 3.1 ± 1 distal anastomoses. Repeated coronarography had to be performed in 28 ± 11 months after surgery because both of the clinical symptoms and novum ischemia on ECG. We determined the proportion of open LIMA grafts and analyzed the cases with signs of LIMA graft insufficiency.

Narrowing of the native coronary artery and graft permeability were determined by independent experts in accordance with the recommendations by AHA. The most severe narrowing in the vessel's diameter located proximally to the site of anastomosis was considered as the narrowing of the target coronary branch.

Quantitative and qualitative coronary angiography (QCA) measurements were carried out in all of the patients, from several projections using Philips Integris software. We calculated the reference diameters, minimum vessel diameters and stenosis diameters. Calibration was performed using a guide catheter. The measurements were carried out retrospectively, on the basis of both preoperative angiography and index angiography, obtained during repeated catheterization. Competitive flow was determined based on the method by Nakajima et al. Selection criteria for the study included performing LIMA angiography.

Prior to measuring fractional flow reserve (FFR), we administered 5000 U of heparin intravenously and inserted a left coronary guide catheter into the origin of the left coronary artery. The patients were given 100 µg nitroglycerine into their coronary

artery and a guide wire of 0.014 inch in diameter fitted with a pressure sensor at its end (Pressure Wire, Radi Medical System, Uppsala, Sweden) was positioned to the end of the guide catheter. Under these conditions (following equalization) the values of pressure were identical. The wire was then guided into the coronary artery. In order to induce maximum hyperemia, 100 µg adenosine was administered into the patients' coronary arteries. FFR was calculated from the Pd/Pa rate, where Pd and Pa represented the mean pressure measured distally from the site of narrowing and the mean pressure in the aorta, respectively.

RESULTS I.

In the first part of the study, all of the selected patients were fitted with bare-metal stents in PCI. The mean diameter and length of the stents were 3.33 ± 0.68 and 22.63 ± 8.86 mm, respectively. A total of 64 stents were used for recanalization as follows: LAD-26 pcs, CX-10 pcs and RCA-21 pcs. Based on Rentrop's classification, no significant collateral circulation was detected during angiography, the extent of collateralization was (0-1).

Analysis of the 57 x 16 (912) segments revealed that 341 segments at risk were detected by angiography, while disturbed wall movement could be identified in 206 segments using echocardiography. On the basis of our definition, using the 16-segment model and regarding echocardiography to be the gold standard, 149 segments turned out to be true-positive. In those cases, echocardiography detected disturbed wall motion in accordance with the site of occlusion in the coronary artery. The number of false negative segments exhibiting disturbed wall motion outside the area of risk was 57. Although they belonged to the area supplied by an occluded coronary vessel, no change in wall motion was detected in 193 segments – they were regarded

false positive. The remaining 513 segments were true negative. Interpreting the data above, the positive predictive value was found to be 0.47, which meant that concerning circulation in segments found to be at risk using angiography, echocardiography also confirmed disturbed wall motion in 47% of the cases. The negative predictive value for disturbed wall motion was 0.9, i.e. in segments in which coronarography justified no risk due to loss of perfusion. In the majority of cases, echocardiography revealed no disturbance either. Low positive predictive value in this case meant that abnormal wall motion was detectable in just a part of the region affected by occlusion, which could be explained by the presence of collaterals.

Regression analysis of the relationship between disturbed wall motion and ischemic time, based on echocardiography performed on admission, led to the conclusion that on-admission-results showed no significant correlation with the length of time from the beginning of clinical symptoms until revascularization, i.e. the proportion of the actual size of the disturbed area and that of the area at risk. Checking the degree of improvement considering the differences between ischemic time and regional wall motion score indices (rWMSI) calculated on admission and during follow-found up, we found significant correlation between the improvement of wall movement and ischemic time ($r = -0.29$, $p < 0.03$).

Next, the patients were divided into two groups based on the length of time between the beginning of clinical symptoms and revascularization as follows: 33 patients within 3 hours and 24 patients in more than 3 hours after the presentation of symptoms. Together with the measured left ventricular EDDs and ESDs, we also analyzed left ventricular ejection fractions calculated on the basis of echocardiography on admission and during the follow-up period.

In the patients undergoing PCI within three hours after the presentation of symptoms ('early group'), significant improvement of the EF was detected during the

follow-up (49.85 ± 5.3 vs $52.41 \pm 7.7\%$, $p=0.04$) but no significant changes in EDD (51.66 ± 4.9 vs 52.91 ± 6.0 mm, $p=0.24$) or ESD (34.56 ± 4.7 vs 35.72 ± 6.1 mm, $p=0.29$) were found.

In case PCI was performed more than three hours later from the presentation of clinical symptoms ('late group') significant increase in EDD (52.17 ± 4.9 vs 55.91 ± 5.5 mm, $p<0.01$) and ESD (35.65 ± 6.6 vs 37.83 ± 7.2 mm, $p=0.04$) could be noted while EF values (47.0 ± 6.8 vs 47.88 ± 7.5 %, $p=0.53$) did not improve significantly.

There was no significant difference in left ventricular function between the two groups on admission (early vs late: 49.85 ± 5.3 % vs 47.0 ± 6.8 %, $p=0.07$) but the EF calculated on examination during the follow-up showed substantial improvement in the early group (52.41 ± 7.7 vs 47.88 ± 7.5 %, $p=0.03$). In the two groups, neither the EDD nor ESD values (51.66 ± 4.9 vs 52.17 ± 4.9 mm, $p=0.70$ and 34.56 ± 4.7 vs 35.65 ± 6.6 mm, $p=0.46$) were suggestive of significant differences on admission to hospital. The above parameters did not change significantly in the early group, but the increase in EDD and ESD in late group was significant. Significant difference in EDDs arose in the two groups (52.91 ± 6.0 vs 55.91 ± 5.5 mm, $p=0.03$) while ESD values (35.72 ± 6.1 vs 37.83 ± 7.2 mm, $p=0.25$) were not significantly different.

RESULTS II.

In the second part of the study, we paid attention to the manifestations of LIMA graft insufficiency. In 6% of the patients included in the study, we observed diffuse graft atrophy (string sign). Cases showing signs of LIMA graft insufficiency were also analyzed individually.

In one of the six cases, string sign developed due to a thick, inappropriately ligated collateral of the LIMA.

In two cases, hemodynamically insignificant (50-60%) narrowing of the LAD portion before the LIMA-LAD anastomosis contributed to LIMA graft degeneration. This was confirmed by QCA and FFR measurements. In one case, $FFR=0.83$ was measured in the LAD. In the other case, the quantitative analysis of the LAD revealed narrowing of the diameter of the vessel by 57%. In contrast, the fractional flow reserve, measured on the basis of the gradient between the two sides of the lesion by the pressure wire during vasodilatation, confirmed non-significant stenosis at 0.89, supporting the presence of competitive flow in the LAD.

In three cases, competitive flow was attributed to relatively rare causes leading to the development of the string sign. In one of these cases, LIMA degeneration was caused by competitive flow due to the radial artery graft stitched to the vessel behind the stenosis located distally to the LIMA-LAD anastomosis.

Rarely, plaque regression might also lead to graft degeneration, as it was seen in one case, in which the plaque, thought to be significant earlier, regressed, thus improving flow through the LAD and creating competitive flow.

In a specific case, the portion of the sequentially stitched LIMA-LAD/diagonal branch-bypass between the LAD and the diagonal branch, bypassed the stenosis in the LAD, thus causing competitive flow against the proximal portion of the LIMA.

DISCUSSION

Based on their MRI investigations, certain authors claimed that the lateral expansion of the area at risk developed in the first hour in STEMI, and, after that, transmural spread of the necrosis was mostly observed. According to others, the score system was easily applicable but they missed reference tests.

Based on our data, the extent and severity of wall motion disturbance compared to the size of the area supplied by the occluded coronary vessel was not dependent on the appearance of clinical symptoms in the first six hours from the beginning of the infarction, i.e. the length of time between the occlusion of the coronary vessel and primary intervention (also referred to as ischemic, or pain-to-balloon time). In patients with similar histories, wall motion disturbance detected using 2D echocardiography occasionally revealed significant differences. In all likelihood, major individual differences could be explained by other factors, such as the ischemic tolerance of the affected myocardium, development of the collateral vascular network or its other, metabolic features.

We compared our results with the experimental model, mentioned in the introduction, in which coronary artery ligation was carried out in dogs' hearts. In animal trials, the extent of wall motion disturbance was checked in 0 minute after the occlusion, at ten-minute intervals in the first hour and a half, and at half-hour intervals in the rest of the six-hour trial. As it was observed, wall motion abnormality had developed by the tenth minute and it did not change over the rest of the trial period. In the current clinical trial, the beginning of symptoms (typically the appearance of chest pain) represented the time of occlusion, while ischemic time was correlated with the completion of catheterization.

By our examinations we could confirm the hypothesis that there was a close correlation between ischemic time and the improvement in wall motion disturbance. Results of echocardiography obtained in three months after the acute event were directly suggestive of how PCI contributed to subsequent improvement by the speed at which blood flow in the coronary vessels was restored. Based on their follow-up echocardiography results, patients who had undergone early PCI and whose revascularization therefore could also be performed earlier, had significant improvement in their condition. Significant improvement in left ventricular function and the fact that there were no substantial changes in left ventricular diameters in the early group could be attributed to successful revascularization, performed in due time, and it also revealed that no essential myocardial remodeling was detected. In the late group, delay before PCI caused global remodeling which manifested itself in a significant increase in left ventricular diameters and non-improving EF. The sooner primary PCI was performed the better the results were on follow-up; there was some improvement in wall motion disturbance in the area supplied by the occluded coronary branch. Based on the results of follow-up examinations, remodeling led to significant differences in EDD and EF between the two groups if revascularization was performed late.

The clinical importance of determining the area of risk is that its size is an independent predictor of the size of the area of infarction and, probably, as a result, also of mortality. However, when one wants to accurately find out about the efficiency of the simultaneous use of additional therapeutic options (e.g. use of glycoprotein IIb/IIIa inhibitors, aspiration of the thrombus and stem cell therapy) and revascularization of the acute infarction it is a must to compare the sizes of the area of risk and that of the infarction.

The current study points out the importance and expedience of integrated evaluation of different therapies and their efficiency in treating myocardial infarction. It is only a comparison as complex as this one that can give exact results in correlating therapeutic methods.

In the second part of the study, we investigated into the incidence of the string phenomenon on LIMA grafts 2-4 years after coronary bypass surgery and analyzed the role of competitive flow in the individual cases.

The LIMA/RIMA are optimal grafts in performing CABG as, practically speaking, they are affected by atherosclerosis to a little extent and the chances of their staying open for a long time are quite good. However, diffuse or distal thinning, known as the string sign, may occur and eventually result in graft insufficiency. It is an established fact, that competitive flow develops between the native artery and the graft if the grafted artery is affected by a slight or moderate lesion. There is extensive clinical evidence confirming that IMA diameter decreases due to competitive flow, which may cause graft insufficiency. This is a multifactorial event, therefore it is difficult to predict its long-term effect, especially when only results of preoperative coronarography are considered. A study published earlier suggested two potential causes leading to the development of the IMA string sign: retrograde systolic flow and low diastolic flow. These changes may be controlled by endothelial changes in the presence of any stimulus.

The LIMA was affected by string sign in six patients (6%) in the patient population during the period of selection. Coronarography confirmed competitive flow in all of the six cases, which was identified as the actual cause of the condition. In cases affecting the LAD, with no redo grafts, QCA confirmed 31-57 % decrease in diameter in the LAD, proximally to the graft. Two patients also underwent FFR measurements in order to exclude significance, the results being 0.83 and 0.89. In

three out of the six cases, FFR or QCA confirmed non-significant lesions. FFR values, calculated from values of coronary pressure, are exact, lesion-specific parameters in deciding whether or not stenosis can cause reversible ischemia. The value of FFR below the (0.75)-0.80 threshold level is a straightforward sign of significant ischemia during exertion. Comparing the results in the literature to our ones it can be concluded that FFR measurements are a potential means in assessing the functional status of lesions and decide whether or not the lesion requires grafting.

In three cases, we identified a relatively rare cause of competitive flow each, leading to the development of string sign: new radial artery on the LAD, significant plaque regression in the native artery and using a sequential LIMA graft on a non-significant diagonal branch.

Our results suggest, that the string sign most commonly appears in the presence of a functionally non-significant lesion, but other causes leading to competitive flow can also be considered. Although investigation into the occlusion of a graft stitched to a non-significant lesion did not appear clinically relevant on the basis of previous observations, circumspect evaluation of individual lesions to be grafted is necessary as early bypassing may provoke graft degeneration without exerting any positive effect on the progression of the lesion.

SUMMARY

Unfortunately, ischemic heart disease, superimposed upon coronary disease, belongs to the leading causes of death even today. In both acute and chronic ischemia, the primary goal is to recognize and properly treat the condition as soon as possible as preserving myocardial viability is a must. In acute myocardial infarction it is time (known as ischemic time) that plays a key role while in chronic ischemia, better clinical outcome can be ensured by means of the long term permeability of the implanted grafts in CABG surgery.

In our project we conclude the following as new results:

1.) Comparing our results with those of the literature, we were the first to demonstrate in a human population that the size and severity of wall motion disturbance detected within the first six hours after echocardiography did not depend on the length of time between the appearance of symptoms and surgery to open the coronary artery. Differences in the individual cases were found, however, in the number of segments affected by wall motion disturbance in the areas at risk. The amount of collaterals in the affected myocardial region or differences in ischemic tolerance may serve as an explanation for the above.

2.) In accordance with previous studies, the results of echocardiography follow-up showed that improvement in disturbed wall motion was greatly dependent on ischemic time and indicated the importance of the time factor between occlusion and revascularization. Our investigations confirmed a previous conclusion: the shorter the time between the beginning of symptoms and intervention, the greater the chance of preventing myocardial dysfunction and, later, remodeling caused by reperfusion following the revascularization of the myocardium.

3.) The integrated approach applicable using HCC software to determine the area at risk – with the inclusion of the results of coronarography and echocardiography obtained on admission and during the follow-up – is suitable to determine the efficiency of different methods in treating acute myocardial infarction.

4.) The degeneration of the IMA graft used in coronary bypass surgery is caused by competitive flow due to different mechanisms. Our results suggest that the string sign commonly develops as a result of an existing non-significant lesion. In order to clarify this suggestion, it is worthwhile to perform QCA, or even pressure wire measurements to determine the extent of stenosis and, also, FFR. It is really important that, prior to insertion into the affected vascular region, the LIMA is properly prepared, its side branches are ligated – all in order to prevent early or late graft degeneration.

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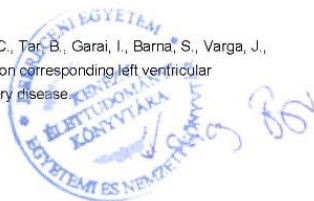
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List of publications related to the dissertation

1. **Rácz, I.**, Fülöp, L., Kolozsvári, R., Szabó, G. T., Bódi, A., Péter, A., Kertész, A. B., Hegedűs, I., Édes, I., Balkay, L., Kőszegi, Z.: Wall motion changes in myocardial infarction in relation to the time elapsed from symptoms until revascularization.
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