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Clinical value of procedures in invasive cardiology for the assessment and relief of myocardial ischemia

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Summary of PhD thesis

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1 INTRODUCTION

The severity and consequences of myocardial ischemia is influenced by several anatomical, pathophysiological, and pharmacological factors. Diversity of the clinical appearance of CAD is primarily determined by (1) variability of progression of coronary artery atherosclerosis, (2) different functional significance of apparently similar coronary stenoses, (3) influence of specific metabolic and pathophysiologic conditions of the heart on adaptation to myocardial ischemia, and (4) pharmacological modification of the ischemic response. Coronary angiography is still the most accepted standard means for assessing the progression of atherosclerotic plaque formation, however, due to its invasive nature, repeated cardiac catheterizations can not be a routine method for the follow-up of progression of CAD. A reliable stress test, e.g DET would obviously be valuable for the non-invasive prediction of progression of CAD, and for the optimal timing of repeated catheterization in symptomatic patients with previously detected CAD.

However, DET might be inferior to other non-invasive methods targeting a specific vessel segment in post-PCI cases of possible restenosis. Theoretically, CFR measurement by TEE can be used for a semi-invasive follow-up for functional evaluation and prediction of long-term success of PCI. Systematic use of STEE for follow-up of post-PCI patients can help us selecting subjects with significant restenosis and high-risk ischemia and referring them to a repeated invasive study.

The diverse clinical appearance of CAD is resulted not only from the variable nature of atherosclerosis progression and/or restenosis process, but also from the individual differences in response of myocardium to ischemia. This is, at least in part, due to the preconditioned state of the myocardium to ischemia. One of the human models of ischemic preconditioning most frequently applied in humans is PCI, where, consecutive brief periods of balloon inflation provide an opportunity to perform and assess the effects of preconditioning.

Although preconditioning provides a remarkable cardioprotection, its effectiveness is attenuated in some animal models of diseases, including hyperlipidemia, diabetes, nitrate tolerance, heart failure, and aging. Among these factors, little is known about the effects of hypercholesterolemia on preconditioning in humans. Not only short ischemic episodes, but additionally certain pharmacological agents can also precondition the

myocardium. This phenomenon is termed 'pharmacological preconditioning'. There is strong evidence, that the protection associated with preconditioning involves the early release of bradykinin and the subsequent activation of bradykinin B2 receptors. The protective effect of intracoronary infusions of bradykinin, administered prior to angioplasty, has been described in patients with severe coronary artery disease. These results suggest that locally administered ACE inhibitors have beneficial effects against myocardial ischemia in both acute coronary syndromes and chronic conditions of ischemic heart disease.

Overall, the aim of thesis was to determine the clinical value of different procedures in invasive cardiology for the accurate and case-specific assessment and mechanical or parmacological relief of myocardial ischemia in the variable environment of CAD progression and ischemia sensitivity.

2 PRIMARY GOALS OF THE THESIS

1. The great variability and the unpredictable nature of atherosclerosis progression makes difficult to plan the regular invasive follow-up of patients with borderline coronary artery stenoses and/or diffuse atherosclerotic disease. Two series of clinical investigations were performed to work out a less invasive follow-up strategy in patients with CAD.

    a) Analysis of the results of repeated dipyridamole-stress echocardiography to predict the angiographic progression of coronary artery disease.

    b) Repeated semi-invasive coronary flow velocity reserve measurements by transoesophageal echocardiography for prediction of restenosis following PCI.

2. With the human experimental model of ischemic and pharmacologic preconditioning we intended to prove that

    a) The adaptive response of the myocardium to ischemia is attenuated by different pathologic states, eg. hypercholesterolemia.

    b) Pharmacologic stimuli – e.g. ACE inhibitor pretreatment – may have a potential for improving the protective effect of ischemic preconditioning.

3 METHODS

3.1. Study populations and protocols

3.1.1. Non-invasive prediction of angiographic progression of coronary artery disease by dipyridamole-stress echocardiography: A series of 60 patients were selected for whom DET and diagnostic coronary angiography had been repeated over a period of 15 years. Echocardiograms and coronary angiograms were recorded and interpreted independently by separate reviewers blinded to the results of the other tests.

3.1.2. The coronary flow velocity reserve measured by stress transoesophageal echocardiography evaluates the success of coronary interventions: The population of 31 patients underwent LAD-PCI including bare-metal stent implantation. STEE was performed on average 8±13 days before PCI and on average 5±4 weeks after it. A third control STEE examination was also performed, 33±20 weeks after the successful PCI. All patients were controlled and undergone telephone consultation 58±10 months after PCI.

3.1.3. The effect of hypercholesterolemia on anti-ischemic effect of preconditioning during coronary angioplasty: The investigations were carried out in single-vessel coronary disease patients elected for PCI. Following exclusion of patients not eligible for the study, 15-15 patients were classified into normocholesterolemic and hypercholesterolemic.

3.1.4. Myocardial protection with enalaprilat in patients unresponsive to ischemic preconditioning during percutaneous coronary intervention: Patients referred for elective PCI with stable angina and single-vessel coronary artery disease were selected for the study. The 20 patients included in the investigation were randomly allocated to either the control group or the enalaprilat group, in such a way that each group contained 10 patients.

3.2. Diagnostic and interventional methods applied in the studies

3.2.1. Coronary angiography

Diagnostic coronary arteriography was carried out with the use of standardized projections. All coronary arteriograms were reviewed and analysed visually by two independent observers. The stenosis was considered significant in the event of a lumen area reduction > 75%. For the

study to evaluate prediction of angiographic progression of coronary artery disease, for any given stenosis and both angiograms, QCA measurement was performed by an automatic edge-detection system. On the basis of a-priori criteria, patients were defined as angiographic progressors if any progression of stenosis was detected visually and if there was any stenosis >30% for which >20% progression of stenosis was measured by quantitative coronary angiography. The extent of CAD was also evaluated by means of the Duke scoring system.

3.2.2. PCI protocol

A percutaneous femoral or transradial approach was used for PCI. The coronary artery lesion was crossed with PCI guidewire. Patients underwent repeated balloon inflations, with periods of reperfusion. In the preconditioning studies, completeness of the coronary occlusion was assessed by a short injection of contrast material. In the study to evaluate the protective effect of enalaprilate, a continuous intracoronary infusion of saline (control group; n = 10) or enalaprilat (enalaprilat group; n = 10) was started immediately after deflation of the first balloon occlusion using the guiding catheter. After cessation of the second inflation, the study protocol was terminated.

3.2.3. Quantitative assessment of myocardial ischemia during PCI

Myocardial ischemia was assessed by measurement of the intracoronary ST-segment elevation by lead C1 of the ECG monitoring system connected to the coronary guidewire. Intracoronary ECG, and intraaortic blood-pressure signals were recorded online, and then every beat was evaluated by an independent physician in a blinded arrangement. The total ischemic burden was characterized by measuring the mean ST-segment deviation (mV) and the peak ST-segment elevation (mV). The dynamics of the evolution of ischemia was characterized with the time to reach 0.5 mV ST-segment elevation.

3.2.4. Transthoracic and stress transoesophageal echocardiography

The left ventricular internal dimensions were measured by 2-dimensional directed M-mode transthoracic echocardiography. The ejection fraction was calculated by the method of Teichholz et al. TEE-derived CFR measurements were carried out according to the standard protocol proposed by Iliceto et al. The coronary flow waveform in the LAD was recorded by pulsed Doppler. Flow measurements were made under baseline conditions

and after the administration of 0.56 mg/kg dipyridamole during 4 minutes. The CFR was calculated as the ratio of the APV during hyperemia to the resting APV.

3.2.4.1. DET protocol

Two-dimensional echocardiographic and electrocardiographic monitoring were performed in combination with infusion of dipyridamole at an initial rate of 0.56 mg/kg over 4 min. Two-dimensional echocardiograms were continuously obtained. Echocardiographic diagnostic end point was the development of obvious echocardiographic positivity. Regional wall motion was assessed, and the wall-motion-score index was derived. According to DET criteria, progressors were defined according to the satisfaction of at least one of two criteria: (1) a negative result of DET in initial testing and a positive result of DET in second testing; (2) positive results both of initial and of second tests, with the latter having a peak WMSI 0.12 greater than that in the former.

3.3. Statistical analysis

Statistical analysis was performed by using analysis of variance or the two-tailed Student's t test for paired data as appropriate. The unpaired t test was applied for between group comparisons. For dichotomous variables, Fisher's exact test was used. Data are reported as means±standard deviation. Correlation of [kappa] indices was used when appropriate. The sensitivity, specificity and positive and negative predictive value were calculating using standard formulae. In the DET study, ROC analysis was performed to identify the stress-echocardiographic parameter providing the best accuracy. To establish the predictive power of the CFR early after PCI, ROC curve was constructed and the area under curve was reported. For the preconditioning studies, the effects of repeated occlusions were analyzed by RM-ANOVA. Confidence intervals in pairwise comparisons were adjusted to multiplications according to the Sidak formula.

4 MAIN RESULTS

4.1. Non-invasive prediction of angiographic progression of coronary artery disease by dipyridamole-stress echocardiography

The coefficient of agreement (κ) with coronary angiography was poor for resting echocardiography (κ=0.144), moderately high for clinical variables

(κ=0.266), and substantial for stress echocardiography (κ=0.764). The concordance of stress-echocardiographic data with respect to coronary-angiography progressors was found 89%. The remaining patients were 'non-progressors' in terms of stress-echocardiographic criteria. An excellent rate of concordance was achieved with a positive DET response becoming negative (100%) and with a negative DET response becoming positive (95%). The concordance was 100% for patients for whom the peak variations in WMSI and DET were chosen post hoc on the basis of ROC analysis. Sensitivity of the 'progressor-pattern' of stress-echocardiography test for predicting progression of CAD was 87%, specificity was 93%, positive predictive value was 96%, negative predictive value was 77% and accuracy was 90%.

4.2. Coronary flow velocity reserve measured by stress transoesophageal echocardiography evaluates the success of coronary interventions

The CFR early after PCI was found to exhibit good prognostic value in predicting patients with reintervention (ROC area:78%, $p<0.05$). The CFR<1.87 was found to have optimal accuracy selected as cut-off value with 69% sensitivity and 86% specificity. From patients who required rePCI or CABG, two patients died: one of them from acute anterior myocardial infarction 29 months after the PCI. From group 2, only one patient had a non-fatal myocardial infarction 30 months after PCI, no other coronary events were found in this group. New coronary interventions were not performed within the 5-year follow-up in group 2 and after the rePCI or CABG in group 1; all living patients are clinically stable now.

4.3. The effect of hypercholesterolemia on anti-ischemic effect of preconditioning during coronary angioplasty

In the normocholesterolemic group, ST-segment elevation showed a continuous rise. Repeated occlusions resulted in lower ST-segment elevations, showing the anti-ischemic effect of preconditioning. In the hypercholesterolemic group, a rapid elevation of the ST segment was developed, which was not observed in the subsequent two occlusions. From 45 to 120 s of the occlusions, there was no difference between ST-segment elevations. This shows that in hypercholesterolemic patients, preconditioning only slowed down the rapid onset of ischemia seen at the initial phase of the first occlusion but did not protect against the evolution of ST-segment elevation observed by the end of the occlusions. In

normocholesterolemic patients, we observed a significant decrease in time to normalization of the ST segment during repeated reperfusions, while in the hypercholesterolemic group, this time was significantly prolonged after all the three ischemic periods as compared to the normocholesterolemic group.

4.4. Myocardial protection with enalaprilat in patients unresponsive to ischemic preconditioning during percutaneous coronary intervention

In the control patients without drug treatment, both the magnitude of the peak ST-segment elevation and the time course of ischemia development were almost identical during the first and second balloon inflations. In contrast, in the patients infused with enalaprilat the peak ST-segment elevation was significantly less, and the time to reach the 0.5 mV elevation was significantly longer during the second than during the first occlusion. The total ischemic burden during the first and second balloon inflations were similar in the control group whereas in the enalaprilat group this was significantly lower during the second occlusion.

5 DISCUSSION

The main interests of these studies were to examine the variability of myocardial ischemia and its clinical appearance. This is manifested in the non-linear progression of coronary atherosclerosis, and in the limited predictability of post-PCI restenosis, as well. Another principal manifestation of this variability is the diverse adaptation capability of the myocardium to ischemia.

5.1. Non-invasive quantification of myocardial ischemia to improve the timing of repeated cardiac catheterization.

The first two of our studies proved that both DET and STEE can correctly predict the progression of native coronary artery disease or the restenosis process. Both of these non-invasive tests can be of great benefit for the invasive cardiologist to correctly assess the indication of repeated cardiac catheterization.

Serial assessment of repeated DET results allows one to separate angiographic progressors and non-progressors efficiently. The unique feature of the present study is that coronary-angiography and stress-echocardiography results were not only assessed horizontally, at one point

in time, comparing different patients, but at two different times, using each patient as his or her own control in order to assess individual variations in anatomic angiographic progression and results of functional stress testing.

Our second study on STEE-derived CFR in the evaluation of the long-term success of LAD-PCI proved that the clinical state of patients with functionally successful PCI improved and these cases did not require further invasive procedures during a 5-year follow-up period. Patients whose condition required rePCI or CABG within half a year, CFR remained unchanged and two patients died during this follow-up period. The TEE–CFR may serve as a noninvasive index of early postangioplasty restenosis.

5.2. Limitation of ischemic preconditioning by hypercholesterolemia and pharmacological enhancement of myocardial ischemic adaptation

Our results proved that in patients with hypercholesterolemia ischemic preconditioning is limited compared to those with normal cholesterol blood level. This observation is a partial explanation of the interindividual variability of preconditioning, however it must be considered clinically important, because this raise attention to the fact that hyperlipidemia is a “double” risk factor; not only that of coronary atherosclerosis, but for the severity of myocardial ischemia, as well. We have shown here for the first time in the literature that in hypercholesterolemic patients, there is a rapid elevation of ST segment during the initial phase of coronary occlsuion, a phenomenon not seen in normocholesterolemic patients. Our results further show that in hypercholesterolemic patients, repeated occlusions although abolished the initial rapid elevation of ST segment but did not attenuate the maximum ST-segment elevation, and failed to decrease the time to normalization of ST segment after balloon deflations when compared to normocholesterolemic patients. These results provide evidence that hypercholesterolemia enhances the evolution of myocardial ischemia on coronary occlusion and significantly inhibits the antiischemic effect of preconditioning in humans. It should be noted here that similarly to hypercholesterolemic patients, in patients with other diseases such as diabetes, heart failure, and aging, the time course of ischemia during PCI may also be altered that can be assessed by a beat-to-beat analysis of ST-segment elevation.

This variability of adaptive response to ischemia of myocardium emphasizes the importance of therapeutic methods improving the efficacy of ischemic preconditioning. The last phase of our research investigated the

therapeutic aspects of the diversity in ischemic preconditioning. We attempted to decrease the variability of myocardial adaptation to ischemia by pharmacological potentiation of the ischemic preconditioning in patients undergoing PCI. The results of this study proved that the myocardium of patients with limited ischemic preconditioning can still be protected by combination of the short ischemic episodes with intracoronary enalaprilate infusion.

The finding of this study supports our previous observation that in patients with severe coronary artery disease who undergo elective PCI, a single brief (2-min) period of balloon inflation is not sufficient to give rise to significant improvements in the intracoronary ST-segment changes that occur during a subsequent, similar period of balloon inflation. We have now demonstrated for the first time that the administration of enalaprilat to such patients during PCI does induce protection, as revealed by significant reductions in the mean and peak ST-segment elevation and the onset of ischemic changes during the second coronary artery occlusion. We consider, that this timing of the drug administration could be of particular importance in everyday clinical practice, since, a variable degree of myocardial ischemia is already present in a substantial proportion of patients with acute coronary syndromes who are referred for emergency PCI. In this patient subset, persistence of ischemic symptoms demonstrate considerably jeopardized state of the myocardium and, limited preconditioning effect of the sequential short ischemic episodes. Our results served indirect information that in these high-risk patients – particularly in those with slow flow and no-reflow phenomenon - the administration of intracoronary enalaprilat can still be cardioprotective.

6 CONCLUSIONS (NEW OBSERVATIONS)

1. Spontaneous evolution of angiographically assessed coronary artery disease can usefully be monitored non-invasively through variations in serial dipyridamole-stress echocardiography. This technique is highly feasible, widely available, of low cost, employing non-ionizing energy. This application can further contribute to the expanding use of stress echocardiography in the cardiological practice.

2. CFR is significantly higher early after functionally successful PCI as assessed by STEE. CFR of patients with successful LAD-PCI increased to >2 and they suffered no major clinical events during the follow-up. In contrast, in those *a priori* had a low CFR and no improvement after PCI, further invasive procedures and major events did occur during this period.

3. Hypercholesterolemia attenuates the anti-ischemic effect of preconditioning, accelerates the evolution of myocardial ischemia, and delays the recovery from ischemia on reperfusion in patients undergoing elective PCI.

4. There is a population of patients with severe coronary artery disease and assigned to elective PCI in whom a brief period of coronary occlusion fails to produce protection against the consequences of a subsequent, similar period of ischemia. We have shown that, in these patients who seem to be unresponsive to this initial preconditioning ischemia, administration of intracoronary enalaprilat during the procedure can still elicit adequate protection.

ABBREVIATIONS

ACE:	angiotensin converting enzyme
APV:	average peak diastolic flow velocity
ATP:	adenosine triphosphate
CABG:	coronary artery bypass graft
CAD:	coronary artery disease
CFR:	coronary flow reserve
DET:	dipyridamole-stress echocardiography
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
LAD:	left anterior descending

LV:	left ventricle
LVEF:	left ventricular ejection fraction
NYHA:	New York Heart Association
PCI:	percutaneous coronary intervention
RM-ANOVA:	repeated measures analysis of variance
ROC:	receiver-operating characteristics
STEE:	stress transesophageal echocardiography
TEE:	transesophageal echocardiography
WMSI:	wall-motion-score index

7 LIST OF PUBLICATIONS RELATED TO THE THESIS

Full papers

I. **Rodriguez O, Picano E, Fedele S, Morelos M, Marzilli M, *Ungi I.*** Non-invasive prediction of angiographic progression of coronary artery disease by dipyridamole-stress echocardiography. Coron Artery Dis 2001; 12(3): 197-204. (IF: 1,098)

II. **Nemes A, Forster T, *Ungi I*, Nagy V, Vass A, Pálinkás A, Varga A, Csanády M.** The coronary flow velocity reserve measured by stress transoesophageal echocardiography evaluates the success of coronary interventions--results of a 5-year follow-up. Scand Cardiovasc J 2005; 39(5): 286-292. (IF:0,757)

III. ***Ungi I*, Ungi T, Ruzsa Z, Nagy E, Zimmermann Z, Csont T, Ferdinandy P.** Hypercholesterolemia attenuates the anti-ischemic effect of preconditioning during coronary angioplasty. Chest 2005; 128(3): 1623-1628. (IF: 4,008)

IV. ***Ungi I*, Pálinkás A, Nemes A, Ungi T, Thury A, Sepp R, Horváth T, Forster T, Végh Á.** Myocardial protection with enalaprilat in patients unresponsive to ischemic preconditioning during percutaneous coronary intervention. Can J Physiol Pharmacol 2008; 86(12): 827-834. (IF: 1,763)

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2. ***I Ungi,* A Genovesi, R Testa, R Sicari, M Marzilli, E Picano:** Non-invasive prediction of angiographic progression of coronary artery disease by dipyridamole stress echocardiography. Eur Heart J (S):P1244, 1997. (IF: 8,917)
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8. **Zimmermann Zs, *Ungi I,* Csanády M:** A coronaria flow rezerv megítélése videodenzitometriával. Cardiologia Hungarica, 2000.
9. **Nemes A, Palinkas A, Forster T, Varga A, Thury A, *Ungi I,* Csanady M:** The effect of aortic valve replacement on coronary flow reserve in patients with significant aortic stenosis and normal coronary angiogram. Eur H eart J, 2002 23, (Suppl.):250. (IF: 8,917)
10. ***Ungi I,* Vegh A, Ruzsa Z, Zimmermann Zs, Rudas L, Csanady M:** The protective effect of enalaprilat during percutaneous coronary intervention: the potential role of bradykinin. Am J Cardiol, 111H, 2002 (IF: 3,905)
11. ***Ungi I,* Nagy E, Ruzsa Z, Zimmermann Z, Ungi T, Csont T, Ferdinandy P:** Ischemic preconditioning induced by coronary angioplasty in patients: effect of hyperlipidemia. J Mol Cell Cardiol 2004;37:179. (IF: 5,054)

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