Summary of Ph.D. thesis

Computerized quantitative assessment of myocardial perfusion on coronary angiograms

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Introduction

Cardiovascular diseases are the main cause of reduced physical activity, early retirement, and mortality in most of the industrialized countries. The primary representative of this group is called ischemic heart disease (IHD), which means a reduced blood flow capacity of vessels supplying the myocardium. IHD is therefore the most significant disorder affecting the industrialized world, both in terms of morbidity and mortality, as well as with respect to the social, medical and economic consequences.

Optimal perfusion of the myocardial tissue is necessary for supply of oxygen and substrates to maintain contractile function. In the presence of a pathological increase in vascular resistance resulting from a stenosis of an epicardial artery, regulatory mechanisms may become exhausted and blood supply may be insufficient, resulting in myocardial ischemia as myocardial oxygen extraction can only slightly increase in ischemic conditions. Traditionally, identification and treatment of augmented coronary resistance have focused on obstructive atherosclerosis of the large epicardial arteries. However, over the past two decades it has become apparent that augmented vascular resistance in the coronary microcirculation may also be responsible for myocardial ischemia in a number of clinical conditions.

The most important first phase of the diagnostic process of IHD is the careful and thorough establishment of the case history, in which all the symptoms are analyzed. Standard and exercise electrocardiograms (ECG) are additional aids to diagnosis. Coronary angiography is regarded as the “gold standard” of the diagnostic methods of IHD. In this investigation, the entire vascular tree is filled with contrast material and visualized by X-ray.

Percutaneous coronary intervention (PCI) is a branch of therapeutic cardiac catheterization, which serves for reduction or elimination of serious narrowings of the epicardial coronary arteries. One of the most important and rapidly developing fields of PCI is to abort an acute myocardial infarction (AMI) by opening of the infarct related artery to reduce the mortality of this devastating disease. Typically, PCI is performed by threading a thin balloon-tipped catheter from a peripheral artery to an artery of the heart. Assessment of myocardial perfusion has a great importance in risk stratification after AMI and successful PCI.

As the importance of the coronary microcirculation in determining patient outcomes has been demonstrated, different quantitative methods for its analysis have been thoroughly studied. Unfortunately, several methods are not routinely applicable in the cardiac catheterization laboratory during primary PCI of the infarct-related artery. Index of microcirculatory resistance (IMR) is a method for the assessment of the status of coronary microcirculation, independent of the epicardial artery. It is derived from distal coronary pressure and hyperemic mean transit time, and is validated in several clinical studies.

A simple clinical tool that describes the effectiveness of myocardial reperfusion was lacking. Therefore, Van't Hof et al. introduced the first angiographic grading method for the assessment of myocardial perfusion. Myocardial Blush Grade (MBG) was described, based on the observation of maximal contrast density at the area at risk, compared to healthy areas. To validate this new tool, MBG was compared with electrocardiographic, enzymatic and sonographic parameters of the reperfused heart. Two years later, Gibson et al. suggested another grading scale describing temporal characteristics of myocardial contrast intensity called TIMI myocardial perfusion grade (TMP). TMP classifies reperfusion based on the dynamics of contrast clearance. After demonstrating high correlation between recovery of myocardial function after AMI and visual perfusion grading (both MBG and TMP), they have been widely used as an endpoint in clinical studies evaluating effectiveness of interventional tools and other therapeutic methods.

The research for quantitative videodensitometric perfusion assessment had started even before the visual grading was first described in the literature. The primary goal of these studies was to develop an operator independent and quantitative way of myocardial perfusion assessment based on X-ray coronary angiograms, which is the only myocardium imaging modality, widely available during coronary interventions. It has been confirmed that myocardial perfusion can be assessed on human coronary angiograms. Computerized quantitative methods are useful tools to assess perfusion from the contrast density signal in the myocardium. It has been demonstrated that computerized videodensitometric perfusion assessment can be used for risk stratification in AMI.

Computerized methods in general have the limitation that the region of densitometric measurement can only be placed in areas without major coronary vessels, because density of vessels is very intensive, and their signal cannot be eliminated from the time-density curve, recorded in the region of interest. Since epicardial arteries leave only small gaps between each other, the region of measurement is specially limited to such small areas that may not represent the state of the whole myocardial area at risk.

Goals

1. Since no reports have been found so far, to evaluate the two visual grading scales, MBG and TMP on the same population, we have compared these scales against echocardiographic, enzymatic and electrocardiographic signs of recovery after AMI.

2. To solve the limitation of visible vessels overlapping myocardial areas in projection images, we aimed to apply automatic detection and elimination

of coronary arteries from X-ray angiograms. An algorithm was developed, capable of videodensitometric myocardial perfusion assessment with masking of visible vessels. The effect of vessel masking on the sensitivity and specificity of videodensitometry was evaluated.

3. Correlation of myocardium selective videodensitometric measurements with clinical parameters of myocardial perfusion was demonstrated in acute clinical setup in patients with AMI and successful primary PCI.

Patients and methods

Patients

The present prospective study comprised 62 patients with AMI and treated by primary PCI. Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the human research committee of the University of Szeged.

Angiography protocol

Angiograms for densitometric analysis were recorded in a way that phase-matched DSA can be performed on them. Projections were chosen to minimize the superpositioning of non infarction-related myocardium and edge of the diaphragm which usually gives motion artifacts on DSA images. Left anterior descending and left circumflex coronary arteries were recorded in lateral (Left Anterior Oblique 90˚), while right coronary artery was recorded in antero-posterior projection.

Analysis of myocardial perfusion

MBG and TMP were graded in a random sequence independently by two cardiologists experienced in the visual analysis of angiograms, who were blinded to all other clinical data. Final values for each patient were based on consensus between the observers. Patient groups of grades 0 and 1 of both MBG and TMP were unified for the statistical analysis, due to identical definitions in MBG 0 and TMP 1, which is also a common practice in the literature of myocardial blush evaluation.

Vessel masking

Although coronary arteries are filled with an X-ray contrast agent during image acquisition, simple image intensity thresholding cannot separate vessel pixels from those of background at a satisfactory accuracy. Vessel segmentation algorithms therefore generally use feature extraction before thresholding, which enhances image regions based on a certain vesselness probability criterion.

A multi-scale vessel detection algorithm was used as described by Frangi et al. to compute vesselness probability maps for all angiograms. It analyzes the eigenvalues of the Hessian matrices of image locations. The vesselness measure at scale σ measures the contrast between the regions inside and outside the range $(-\sigma, \sigma)$ in the direction in which the local second order structure (curvature) of the image is the greatest. Maximal vesselness values over a range of σ from 1.0 to 5.0 formed the final vesselness maps of angiograms. Vesselness maps were thresholded at 10% of maximal value to generate binary vessel mask images.

Videodensitometric measurement

Time-density curves (TDC) were recorded in polygonal regions of interest, selected by a cardiologist experienced in the analysis of coronary angiograms. Phase matched DSA images were used with stabilized image acquisition parameters for measurements.

The computerized method for myocardial perfusion assessment was based on the analysis of the time-density curves measured over the infarct-related myocardial region of interest (ROI). The polygonal ROIs covered the whole myocardial area at risk for each patient. ImageJ image analysis software (http://rsb.info.nih.gov/ij/) was used for ROI definition and computation of the TDC. Binary vessel mask images were used as a logical mask to exclude image points belonging to vessels from the computation of average density in the ROI. Frequencies higher than 0.6 Hz were removed from the TDC to eliminate artifacts from cyclic heart contractions. G_{max} was defined as maximal amplitude of the TDC, T_{max} is the time to reach G_{max}. Perfusion was characterized with G_{max}/T_{max} according to previous results. The only user interaction needed in this measurement is the definition of the ROI. Therefore, this is the only source of interobserver and intraobserver variability. This variability is evaluated by performing all measurements by two independent, experienced cardiologists.

Clinical indicators of reperfusion

Twelve-lead body-surface electrocardiograms (ECG) were recorded at the beginning of PCI and 90 minutes later. ST-resolution was defined as a decrease of ST-segment at 90' compared to the first measurement in the lead with highest ST-segment elevation, expressed as percentage of initial ST elevation.

Blood creatine-kinase (CK) enzyme levels were measured 6, 12, 24 and 48 hours in the AMI patient population after PCI. These four measurements were summed up to assess cumulative enzyme release, and this sum is used throughout the results section.

Echocardiographic measurements were performed 3 days after the primary PCI to assess left ventricular ejection fraction (LVEF) in the AMI patient population.

Statistical analysis

All statistical tests were performed with MedCalc software package (MedCalc Software, Mariakerke, Belgium). A value of $p < 0.05$ was considered to be statistically significant.

The AMI patient population has been divided into two groups by clinical indicators of successful reperfusion for receiver operating characteristic (ROC) curve analyses. ST resolution >50% and cumulative CK release <5000 U/l were chosen as cut-off values, which divided the population to approximately equal two parts. Our results were obtained by ROC curve analyses at a confidence interval of 95%.

Correlation of G_{max}/T_{max} in elective patients with parameters of perfusion was assessed by Pearson correlation coefficient.

Interobserver variability was analyzed by Bland-Altman method, and linear regression.

Results

1. Visual grades in acute patients

Enzymatic infarct size, as expressed by sum of CK release, had a significant negative correlation ($R=-0.687$, $P<0.001$) with TMP, but not with MBG ($R=-0.062$, $P=0.63$) at our current sample size. A positive, significant correlation was found between echocardiographic left ventricular ejection fraction (LVEF) measured 3 days after PCI and both MBG ($R=0.389$, $P=0.002$) and TMP ($R=0.587$, $P<0.001$). TMP showed stronger correlation. ST-segment resolution as percent decrease of initial ST elevation also correlated with MBG ($R=0.348$, $P=0.006$), but had a stronger correlation with TMP ($R=0.574$, $P<0.001$), which is consistent with the previous findings. In summary, lower perfusion grades were always found to be associated with worse functional parameters of the heart.

The main finding of the comparison of visual grades is that TMP has a stronger correlation to enzymatic infarction size, LVEF and ST-resolution than MBG, however, both grades show the same tendency when compared to other clinical parameters of AMI patients after PCI. These results suggest that clearance dynamics of the dye from the microcirculatory compartment (classified by TMP grade), i.e. the temporal changes of myocardial blush provides more precise information on indicators of myocardial viability than absolute density expressed by MBG, i.e. the spatial variations.

In contrast with these findings, MBG is more widely used in the literature than TMP to evalueate new interventional devices and other therapeutic methods. This may be explained by the historical importance of MBG, since it was the first method to evaluate myocardial tissue perfusion by videodensitometry. TMP was introduced only two years later. Since there was no study comparing the usefulness of the two perfusion grades, there was no evidence on the better prognostic value of TMP grade. Our results suggest that TMP should be used in the clinical practice, rather than MBG.

This result is published in the following papers:

- Ungi T, Sasi V, Ungi I, Forster T, Palkó A, Nemes A. Comparison of two visual angiographic perfusion grades in acute myocardial infarction. Ups J Med Sci. 2009;114(3):149-53.

- Ungi T, Jónás Z, Ungi I, Sasi V, Zimmerman Z, Palkó A. Az akut szívizominfarktus klinikai jellemzőinek összefüggése a szívizom-perfúzió angiográfiás paramétereivel. Magyar Radiologia. 2007; 81(3-4):110-116.

2. Effect of vessel masking on prediction of recovery after AMI

Optimal cut-off values have been determined for TMP and G_{max}/T_{max} with and without vessel masking to predict sum of CK <5000 U/l and ST-resolution >50% in our study population. Individual ROC curves were characterized by sensitivity (Se), specificity (Sp) at the optimal cut-off value, and area under the curve (AUC). G_{max}/T_{max} without vessel masking did not improve results of ROC analysis compared to visually graded TMP neither in the evaluation with cumulative enzyme release, nor in the evaluation with ST-resolution. When vessel masking was applied before G_{max}/T_{max} measurement, an improvement has been observed in almost all ROC parameters both with cumulative enzyme release (AUC increased from 0.76 to 0.84) and with ST-resolution (AUC increased from 0.72 to 0.83).

Our results show that vessel masking improves the sensitivity of videodensitometric myocardial perfusion assessment to detect cumulative enzyme release and ST-resolution after successful primary PCI in AMI. Early resolution of ST-segment elevation is related to restoration of myocardial perfusion, less myocardial damage, and better prognosis after PCI for AMI.

To our knowledge, our presented method is the first to combine vessel masking with perfusion assessment on X-ray coronary angiograms. This allowed us to define ROIs including the whole myocardial area at risk, while arterial contrast density still did not interfere with myocardial density signal analysis.

This result is published in the following paper:

- Ungi T, Zimmermann Z, Balázs E, Lassó A, Ungi I, Forster T, Palkó A, Nemes A. Vessel masking improves densitometric myocardial perfusion assessment. Int J Cardiovasc Imaging. 2009 Mar;25(3):229-36.

3. Validation with other clinical parameters in acute patients

Enzymatic infarct size as expressed by sum of CK release had a significant negative correlation ($R=-0.445$, $P<0.001$) with G_{max}/T_{max}. Additionally, a positive significant ($R=0.364$, $P=0.004$) correlation was found between G_{max}/T_{max} and ST-segment resolution as % decrease of initial ST elevation. A milder, but still significant relationship was found between G_{max}/T_{max} and echocardiographic LVEF measured 3 days after PCI ($R=0.278$, $P=0.029$).

We have confirmed that examination of contrast density in the myocardium with coronary angiography provides important information on myocardial viability, and with this, on the evaluation of true functional success of primary PCI.

This result is published in the following paper:

- Ungi T, Ungi I, Jónás Z, Sasi V, Lassó A, Zimmermann Z, Forster T, Palkó A, Nemes A. Myocardium selective densitometric perfusion assessment after acute myocardial infarction. Cardiovasc Revasc Med. 2009 Jan-Mar;10(1):49-54.

4. Interobserver variability

Plotting G_{max}/T_{max} values on Bland & Altman plot and scatter diagram of two independent observers reveals a reliable interobserver agreement of our method. In the range of low G_{max}/T_{max} values (1 - 2.2), Bland & Altman diagram shows some significant scatter between repeated measurements by different operators. Linear correlation between measurements of different operators is also strong (R=0.98).

This result is published in the following paper:

- Ungi T, Ungi I, Jónás Z, Sasi V, Lassó A, Zimmermann Z, Forster T, Palkó A, Nemes A. Myocardium selective densitometric perfusion assessment after acute myocardial infarction. Cardiovasc Revasc Med. 2009 Jan-Mar;10(1):49-54.

Journal publications related to the theses

1. Ungi T, Sasi V, Ungi I, Forster T, Palkó A, Nemes A. Comparison of two visual angiographic perfusion grades in acute myocardial infarction. Ups J Med Sci. 2009;114(3):149-53.

2. Ungi T, Ungi I, Jónás Z, Sasi V, Lassó A, Zimmermann Z, Forster T, Palkó A, Nemes A. Myocardium selective densitometric perfusion assessment after acute myocardial infarction. Cardiovasc Revasc Med. 2009 Jan-Mar;10(1):49-54.

3. Ungi T, Zimmermann Z, Balázs E, Lassó A, Ungi I, Forster T, Palkó A, Nemes A. Vessel masking improves densitometric myocardial perfusion assessment. Int J Cardiovasc Imaging. 2009 Mar;25(3):229-36.

4. Ungi T, Jónás Z, Ungi I, Sasi V, Zimmerman Z, Palkó A. Correlation of clinical parameters with myocadial perfusion grades in acute myocardial infarct patients. [In Hungarian] Magyar Radiologia. 2007; 81(3-4):110-116.

Other publications related to the theses

1. Ungi T, Novak G, Lasso A, Sasi V, Ungi I. Videodensitometric myocardial perfusion assessment on coronary angiograms. Int J CARS (2009) 4 (Suppl 1):S311-S355.

2. Ungi T, Ungi I, Balázs E, Sasi V, Zimmermann Z, Nemes A. Myocardium selective densitometric perfusion assessment after acute myocardial infarction. European Society of Cardiology (ESC) Congress 2008.