SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

# INTEGRATED EVALUATION OF THE FUNCTIONAL CONSEQUENCES OF CORONARY LESIONS: HOLISTIC APPROACH WITH NON-INVASIVE AND INVASIVE CARDIAC IMAGING TECHNIQUES

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# I. INTRODUCTION

## ○ 2D and 3D imaging techniques

In Hungary, cardiovascular disease is responsible for the highest mortality and morbidity rates, placing a huge burden on people, society and health care. Among patients with a low (<1% annual cardiac mortality assessed by non-invasive examinations) or a high (>3% annual mortality) cardiac risk the negative (NPV) and positive (PPV) predictive values for cardiovascular morbidity are high, and a therapeutic modification or invasive coronary angiography (ICA), respectively, is the preferred approach. For patients in the low-intermediate or intermediate risk group non-invasive imaging is the most accurate approach aimed at ruling out the need for invasive assessment or medical therapy. For years, one of the most sensitive diagnostic modalities for diagnosis of coronary artery disease (CAD) has been myocardial perfusion imaging (MPI), with a sensitivity and specificity of 60-100% and 70-100%, respectively. MPI is a well-established method for obtaining functional information on the myocardium. Stable angina patients with a normal MPI picture are at low risk of a fatal cardiovascular event. (As more regions are affected, the possibility of subsequent cardiac events increases. Accordingly, it is challenging to decide on the further approach when mild perfusion defects are present, especially when no co-morbidities (diabetes mellitus, transient ischemic attack, stroke; left ventricular dilation, etc.) appear in the history. With no or only mild ischemia, medical therapy offers a better survival, whereas patients with moderate-to-severe ischemia benefit more from revascularization.

Recently, new imaging methods have been developed, e.g. 64-slice multi-detector computed tomography (MDCT) and three-dimensional (3D) reconstruction software for data acquired from two-dimensional (2D) imaging devices. As methods and devices further improve, the decision-making physician has more tools in his hands to arrive at a proper conclusion with regards to further approach. As of today, none of these methods offer 100% specificity and sensitivity, which can lead to false-positive and false-negative results, the latter being unacceptable in the clinical practice. When it comes to decision-making, the physician has to use all information that is available to rule out any disease. At the beginning of the evaluation process, it is possible to differentiate between subjective and objective parameters, past medical history and symptoms/complaints of the patient, the latter information being provided by results obtained from diagnostic procedures. When two or more data of different origins exist, integration of all information provides chance to getting closer to proper diagnosis.

When it comes down to full-scale evaluation, the physicians always have to consider the limitations of each method, especially when choosing the next step. Non-invasive methods are always preferable when the desired solution might be obtained through them. Also, availability of anatomical or functional information alone might not be sufficient. Presently, ICA and MDCT are able to show the substrate of possible coronary intervention, earlier considered the gold-standard. Both of them give anatomical information, but provide little or none information on functional properties. The indication for intervention, apart from acute coronary syndrome, should never be based on only anatomical parameters, but rather on the pathophysiology consequences, which can be detected by MPI or echocardiography. The comparison of coronary angiography projected from different views with slices of a 3D tracer distribution of MPI and 2-3D echocardiography images can be rather difficult. The exact *in vivo* determination of the myocardial perfusion area of a particular coronary artery theoretically requires 3D registration of the coronary artery system to the imaged left ventricle. For the time being, this has not been achieved sophistically in clinical practice despite publications of algorithms for assessment of the 3D coronary tree structure. The report on coronary angiography often might not serve as an accurate reference for evaluation of perfusion defects and wall motion abnormalities detected by MPI or echocardiography to find the functional consequence of coronary artery abnormalities. Thus, the need for integration of the anatomical and functional information, with the most accurate identification of the left ventricular regions hypoperfused in association with the detected coronary stenosis, is high.

With the polar-map display (or bull’s-eye image), originally applied at MPI, a comprehensive interpretation of the left ventricle segments is possible. This is a non-rigid registration of the left ventricle segments originally applied for the visual and quantitative analysis of MPI results, in which maximal-count circumferential profiles of well-defined short- and long-axis planes are plotted on a map, showing the distribution of the perfusion tracer onto a 2D polar representation. Each image plane forms a ring in the polar map: the outer annuli of the polar map correspond to the basal regions of myocardium, whereas the inner rings are representing the segments towards the apex. Polar maps can also be normalized to each other or to a database so that direct comparisons can be made. The usual coronary artery distribution is often indicated on the polar maps of SPECT or positron emission tomography (PET) studies by referring to the regions of the three main coronary branches.

In 80% of the cases, the coronary circulation is defined as right-dominant, i.e. the right coronary artery (RCA) provides the posterior descending artery (PDA). However, individual variations may differ extensively. This classification takes into account only the relation between the distributive characteristics of the RCA and left circumflex (LCx) branches, and not variations with regards to the PDA and left anterior descending (LAD) artery in relation to the apex.

In our research we used and completed further development in a piece of software, which applies an integrated evaluation of the imaging results (ICA, echocardiography and SPECT) using the results from patients with coronary artery disease. This semi-quantitative registration of the coronary tree to a polar map focused on the relation between the supplying coronary branches and the myocardial regions of the 16-segment left ventricular model. All the recorded anatomical and functional data were related to these 16 left ventricular segments, which allowed the direct comparison and holistic synthesis of the results.

- **Characteristics of the coronary flow**

About 250-500ml of blood flows through the coronary arteries every minute. In certain ways, the characteristics of coronary flow differ from those of the rest of the body. As above all, most part of the flow takes place during diastole, when the myocardium is at rest. Also, while normally 30% of the oxygen is extracted from the capillary beds, in the heart being about 70%. Last, but not least, the flow in the myocardium is not homogenous: worst in the endocardial segments, mostly due to the pressure from the cavities of the heart.

Maximal blood flow starts to decrease at 50% luminal diameter stenosis, but the resting flow is unaffected until there is more than an 80% decrease. The coronary artery flow is dependent on both systemic (neuronal, hormonal) and local (metabolic, myogenic and tissue pressure processes) control. High capillary-to-myocyte ratio serves best for the metabolic needs of the myocardium, but when it comes to the functional part, the stage of the capillaries and driving pressure gradient becomes important. Should the pressure in the epicardial arteries increase or decrease, the pressure-flow curve keeps a linear or slightly positive slope: this is called autoregulation. Between app. 70-150Hgmm the coronary circulation provides the same perfusion regardless to the pressure. Unfortunately, below the lower range flow decreases steadily, causing severe perfusion defects. Should the pressure go above the upper limit, the flow will increase reasonably. The pressure-flow relationship during maximal vasodilatation is approximately straight, but these parameters can change differently in certain conditions.

Coronary blood flow and coronary resistance are influenced by the epicardial arteries (minimal role when no subtotal stenosis is present), precapillary arterioles (high impact) and subendocardial wall tension. The ability of increasing the blood flow during exercise can be blunted by a pressure gradient developed through a stenosis. To investigate the pressure and flow changes when stenosis is present and to test their relation, two methods are used: coronary flow velocity reserve (CFR) and fractionated flow reserve (FFR) measurements.

CFR provides the capability of the entire coronary system to maintain the flow (both on epicardial and microcirculatory level). Flow velocity in coronary arteries is measured with specific piezo-crystal tipped catheter. Flow and volume are directly proportional when no change in the coronary diameter is present: Q flow = V (mean velocity) x A (area). The measured flows are averaged at baseline and maximum hyperemia. CFR has four baseline characteristics: baseline level of flow, perfusion pressure, cross sectional area (calculated to myocardial volume) and extracoronary flow resistance. The baseline flow is the result of heart rate, ventricular wall tension and contractility. The higher the baseline level, the lower increase is possible. The area, mostly determined by the microvasculature status, will provide the incline when flow is increasing at maximal hyperemia. During exercise (physiological induction of hyperemia) CFR can increase 3-4-fold. CFR values relate closely to quantitative coronary angiographic (QCA) measurements.

Absolute CFR is defined as the ratio of mean hyperemic to mean baseline flow velocity. Relative CRF is the ratio of the CFR in the diseased vessel to the CFR of the non-diseased vessel. When luminal decrease develops, the hyperemic flow and CFR decreases. When CFR <2.0 measured distal to a coronary stenosis, the possibility of significant coronary stenoses is high. When comparing CFR in stenosed and non-stenosed coronary arteries without inhomogeneous coronary capillary disease, the ratio characterizes the effect of the stenosis in the epicardial artery, with normal values ranging from 0.8 to 1.0. Obviously, when there is no non-diseased reference artery (three-vessel disease), or when the microcirculatory system is not „balanced” (regional myocardial necrosis, e.g. post myocardial infarction), the ratio cannot be measured accurately.

FFR is a pressure-derived ratio estimating the pressure changes and the blood flow through a stenotic lesion at maximal hyperemia, and is measured through a wire with pressure sensor at the tip. FFR is independent of hemodynamic conditions, e.g. heart rate, blood pressure or contractility. When compared to CFR, FFR does not need any reference measurement, since all pressures are measured in the same artery. FFR also takes into account the contribution of collateral flow to myocardial perfusion. When well developed collateral flow is present, the FFR can be higher than the stenosis would be capable of producing. Should there be consecutive stenoses, the FFR measured between the two is underestimated by the presence of a distal stenosis. To characterize each FFR decrease caused by the consecutive luminal decreases the wire has to be pulled back and each drop in the pressure has to be presented separately. The "end of the coronary system" is the right atrium, so it always has to be taken into consideration when increased right atrial pressure is present (normal: 0-5Hgmm).

Microvascular disease, both general (diabetes mellitus, endothelial dysfunction, changes caused by smoking, etc.) and local (myocardial infarction, after bypass-grafting certain segments, etc) has an impact on both CFR and FFR. Without reaching maximum hyperemia the CFR and the decrease of the FFR can be underestimated. When hypertrophy of the myocardium develops by age, CFR at any given pressure is less than normal, no matter how flows are measured. With regards to myocardial muscle mass, the total cross-sectional area of the coronary resistance vessels does not increase, indicating that the stage of the pre- and postcapillary sphincters has a high importance in the flow regulation. CFR can also be lower at maximal vasodilatation during polycythemia, diseases of the large or small coronary arteries, tachycardia; increased end-diastolic pressure and at marked increase in contractility. When endothelial dysfunction occurs, the cross sectional area of the coronary bed does not increase, since the autoregulatory effect of the local neurohormonal system is diseased, whereas in ischemic heart disease both area reduction and functional changes occur. When the arterial bed area is decreased, one compensating mechanism of the heart is the angiogenesis of parallel collaterals.

When comparing relative CFR and FFR at maximum vasodilation, the ratios are similar. Due to the equality of the two values in certain conditions and taking into consideration the above factors, CFR measurements are not used in the daily clinical practice, rather FFR is calculated and used as a gatekeeper to intervention.

There are also physical components to the flow changes. The equation that characterizes the severity of the stenosis is as follows:

$$\Delta P = fQ + sQ2,$$

where $\Delta P$ is the pressure gradient, $f$ is the frictional effect factor, $s$ is the separation effect and $Q$ is the flow. The pressure drop is a quadratic function of pressure loss due to viscous friction (f) and flow (Q) separation The viscous friction pressure loss coefficient $f$ is determined by the stenosis length (L) and inversely by the minimal cross-sectional lumen area (MLA): f ~ L / $MLA^2$. The flow separation pressure loss coefficient $s$ is influenced by the geometry of the stenosis (affected by the difference between the MLA and the non-stenotic part of the vessel: s ~ 1/ $MLA^2$ - $AS^2$/ $MLA^2$x$10^4$) and fluid properties of blood. According the Poisseuille's law of laminar flow,

$$\Delta P = \frac{8\mu LQ}{\pi r^4},$$

where $\Delta P$ is the pressure drop, $L$ is the length of pipe, $\mu$ is the dynamic viscosity; $Q$ is the volumetric flow rate, $r$ is the radius, $d$ is the diameter and $\pi$ is the mathematical constant, it is clearly shown that pressure gradient is inversely proportional with the quadratic power of the radius (stenosis), putting high importance on the diameter decrease of the lumen when flow changes occur.

The measurement of FFR, with the use of a guide-wire acquainted with pressure sensor at the tip, is accepted as gold-standard for the objective evaluation of hemodynamic changes caused by coronary artery stenosis, because FFR has showed good correlation with the degree of myocardial ischemia and coronary events. The decision of measuring the possible flow decrease is in the hand of the examiner, but is definitely advisable when the significance of a coronary lesion is not certain, since the hemodynamic effect based on the identification of the degree of diameter stenosis is ambiguous.

FFR is calculated as Pd/Pa: Pa refers to the pressure measured at the tip of the catheter placed in the ostium of the coronary artery, representing the aortic pressure, whereas Pd is the value measured at the tip of the pressure-wire, which should be placed distal to the stenosis. The value <0.75 implies significance, with values between 0.75 and 0.80 considered a "gray zone." This value strongly correlates with ischemia measured by non-invasive methods, and the post-intervention resolution of abnormal FFR also correlates well with resolution of ischemia. Furthermore, there are 5-year prospective and retrospective data demonstrating that interventions on intermediate lesions with FFR of ≥0.75-0.80 can be safely deferred with an annual risk of cardiac death or myocardial infarction <1%. In the DEFER study, FFR was used to determine the need for stenting in patients with intermediate single vessel lesions, stating the outcome only improved when stenting lesions causing FFR <0.75. The FAME study evaluated patients with multi-vessel disease. In one arm the decision of placing the stent was based merely on angiographic evaluation, while in the other arm FFR was measured, and any stenosis causing FFR <0.80 was stented. The one-year primary endpoints of death, nonfatal myocardial ischemia or repeat intervention were lower in the FFR group. Also, hospital stay (3.4 vs. 3.7 days) and the procedural costs ($5,332 vs. $6,007) were lower in the FFR group. With regards to procedure length, it was the same in both groups, meaning that placing the special wire into the coronary artery did not prolong the procedure significantly.

# II. AIMS

In our project we have developed an integrating process for detections of any functionally significant coronary artery stenosis on the basis of the abnormalities associated to the supplying epicardial lesion. With the use of anatomical rules and assumptions of the epicardial surface, we developed a method for the integration of different projections of the coronary artery tree into a two-dimensional polar map display, thus determining the myocardial region associated with a coronary lesion. Previously, the ICA has been the gold-standard for detecting significant coronary artery disease. In our approach, we decided that our intergraded evaluation will serve as a gold-standard, to see how well the information from ICA correlates with the functional and anatomical coupling from other imaging methods.

In the second part of the research we investigated whether there was any correlation between the fractionated flow reserve (FFR) measurements and the volume of the plaque causing the changes in the blood flow. ICA gives high-resolution, good contrast images of even the distal coronary vessels. Due to the perspective deformation of vessels on the conventional 2D images, it has limitations in visualizing the true dimensions of the coronary arteries and lesions. Foreshortening of vessel segments leads to underestimation of actual vessel length and asymmetric stenosis caused by eccentric plaques cannot be evaluated in their complexity. Consequently, 3D interpretation of the actual geometry of the coronary tree designed from multiple projection angels requires reconstruction. With 3D quantitative coronary angiography (QCA) systems using standard 2D images acquired from conventional ICA, 3D images can be reconstructed by dedicated software commercially available as an add-on to angiographic devices. 3D coronary segmentation also provides an opportunity to use orthogonal portraying of the lesion subtracting the over- and underlying structures. Thus, more accurate spatial orientation of lesion can be obtained, which can be useful when choosing the best possible balloons or stents before the intervention, increasing the success of coronary intervention.

As of today, only a few studies have compared the differential capabilities of the anatomical analyses of 3D- and 2D-QCA in predicting functionally significant stenosis as assessed by FFR. The second part of the investigation aimed at comparing 3D-QCA derived quantitative parameters with the functional significance of intermediate coronary artery stenoses as determined by the invasively measured FFR. Few data are available with regards to the parameters produced by the 3D reconstruction of such stenoses and the related FFR value.

# III. PATIENTS

## 1. Integration of imaging techniques with HCC

Ten post-myocardial infarction, stable angina patients' data were analyzed in the investigation (age 48±9 years, 3 females, 7 males, EF: 36,1±7,2%). The infarctions took place 1-6 months prior to the examinations; 14 totally or subtotally occluded coronary branches (6 LAD, 5 RCA, 3 LCx, 6 one-vessel and 4 two-vessel diseases) were involved. According to the conventional classification seven patients had a right dominant, two had left dominant and one had balanced coronary circulation.

## 2. Comparison of 3D plaque reconstruction and FFR

22 patients with stable angina pectoris on full possible anti-angina treatment (7 female, 15 male, age 61±9.73 years) were involved in this study. Hypertension, diabetes mellitus and hypercholesterolemia were in the previous history in 13%, 56% and 69% of the cases, respectively. Three patients had prior myocardial necrosis, but infarction in the supplied myocardial territory of the measured coronary branch was ruled out by echocardiography and MPI. 3D reconstruction was successfully carried out on 23 coronary arteries (14 LAD, 4 CX and 5 RCA). FFR measurements on the same 23 lesions were performed simultaneously with the coronary angiography.

# IV. METHODS

## ○ Invasive coronary angiography

After having the patient sign the informed consent, ICA was performed in local anesthesia from femoral or radial approach. A 6French sheath was placed into the preferred artery, through which Judkin's 6F right and left diagnostic catheters were advanced into the coronary arteries with the help of guidewires. 6-8ml of contrast material for each projections were injected prior to acquisition. Fluoroscopy was provided by Philips Integris and Axiom Artis Siemens devices. The image acquisition and reconstruction was executed at a speed of 12.5 and 15 frame-per-second, respectively. Favorable projections included AP-caudal, RAO-caudal, RAO-cranial, spider-view and left lateral view for the left coronary system, and lateral-view and LAO-cranial for the right coronary system. Based on physician discretion, the projections were tailored to different angles for better image acquisition. No intracoronary nitrate was given until all diagnostic projections had been completed.

## ○ 3D reconstruction

IC30 software from Siemens was used to reconstruct a 3D model of a coronary artery by fusing two or more angiographic images. 2 or 3 ECG-gated end-diastolic frames separated from each other at least 30° were used to reconstruct to segment of interest at the coronary lesion. The guiding catheter was used to calibrate pixel size. The site of the stenosis, the proximal and distal coronary artery segments were manually identified on the images, then the software automatically generated the arterial lumen in 3D. Cross-sectional area percentage stenosis (AS), plaque volume (PV) and minimum luminal area (MLA) were calculated by the sofware from 3D parameters. 2D quantitative analysis was also performed from the views depicting the most severe stenoses to calculate the minimum luminal diameter (MLD) and the percentage diameter stenosis (DS).

## ○ SPECT

Patients were instructed to consume nothing orally overnight. Coffee and medication containing caffeine or aminophyline were withdrawn for at least 12 hours. In the single-day protocol dipyridamole (0.56 mg/kg) was administered slowly during 4 minutes. A 3-hour resting period was provided between the two studies. 250 and 750 MBq Technecium $^{99m}$ SestaMIBI was injected intravenously for stress (3 minutes after the dypiridamol injection) and rest examination, respectively. Acquisition was initiated 60-90 minutes after each isotope injections on an APEX HELIX dual-head gamma camera (Elscint) in single-head mode.

Sixty images were acquired in 64×64 matrices (pixel size: 6.9 mm) on a 180° arc from RAO 45° to LAO 45°, using a high-resolution collimator; the image acquisition time was set to 25 sec. Images were reconstructed and evaluated with a dedicated quantitative myocardial perfusion program package (ACSP-2, Elscint) after 2D filtering with a Butterworth filter (parameters: 0.35 and 5) using a ramp-filtered backprojection, with a zoom factor of 2. Three reoriented slice sets (parallel to the short-axis, the horizontal long-axis and the vertical long axis of the left ventricle) were displayed for visual evaluation. The software semi-automatically determined the processing parameters: apical and basal frames, center and radius of the tomograms.

The maximum count circumferential profiles for all of the stress and rest tomograms were automatically sampled, using spherical coordinates to sample the apical region and cylindrical coordinates to sample the remainder of the myocardium. Distance-weighted polar maps were constructed by mapping sequential maximum-count profiles from the apex to the base into successive rings in the polar map (the apex is mapped into the center and the base is mapped into the periphery). Each ring within the polar map was assigned the same width in pixels. The width was determined by dividing the radius of the polar map by the number of sampled segments (spherical rings + cylindrical slices) in the study. From the polar map the average activities of the predefined 16 regions were expressed. The software picked the segment having the highest activity as 100%, and the rest of the activities in the segments were compared to this; <80% was regarded as abnormal perfusion during stress test.

- **Echocardiography**

Echocardiography examinations were performed on Sequoia ultrasound device using 3.5MHz harmonic imaging transducer. End-systolic and diastolic left ventricular diameters were measured, and the ejection fraction was calculated by Simpson rule. Wall motion abnormalities were evaluated using the 16-segment model. A joint paper from the American Heart Association, the American College of Cardiology and the Society of Nuclear Medicine defined standards for plane selection and display orientation for serial myocardial slices generated by cardiac 2D or tomography imaging. The cardiac planes generated by using the long-axis of the body do not cleanly transect the ventricles, atria, or myocardial regions supplied by the major coronary arteries. SPECT and 2D–echocardiography have defined and oriented the heart for display at 90° relative to the long-axis of the left ventricle that transects the apex and the center of the mitral valve plane. This approach maintains the integrity of the cardiac chambers and the distribution of coronary arterial blood flow to the myocardium. For these reasons, this approach is optimal for use in research and for clinical work involving cardiac perfusion and function. The names of the planes were as follows: short-axis, vertical long-axis and horizontal long-axis. These correspond to the short-axis, apical 2-chamber, and apical 4-chamber planes traditionally used in 2D echocardiography.

The generally accepted recommendation for the number of myocardial segments for echocardiography is 16. Wall motion was evaluated using this 16-segment scoring system analyzed in blinded fashion without knowledge of patient identity. Evaluation of the segmental wall motion uses 1–5 scores, 1 indicating normokinesia, 2 hypokinesia, 3 akinesia, 4 dykinesia and 5 an aneurysm.

For summarizing the results for the entire left ventricle, the 16-segments can be projected onto a polar map by the same principles as for the nuclear studies. In the local coordinate system of the heart, from the ("reoriented") two- and four-chamber long-axis views, the 6–6 examined segments for each take place along the vertical and the horizontal axes of the polar map. Together with the results of the remaining four segments examined from the parasternal view (the short-axis slices represents the same segments as examined from the long-axis views), all the 16-segments can be projected onto the polar map, which is appropriate for the integrated analysis of different images. When registration of different techniques on the same polar map is performed, the anatomical hallmarks like the apex, the papillary muscles and the junction of the right ventricle can be used.

- ### FFR measurements

Advancing to the coronary ostiums was performed the same way as during ICA. Afterwards, a 6F guiding catheter without side-holes was positioned at the orifice of the left or right coronary artery to detect the proximal (aortic) pressure without damping. The distal pressure was recorded by pressure-sensor guide-wire (PressureWire Certus, Radi Medical). The pressure trace from the semiconductor sensor at the catheter tip was equalized to the fluid-filled pressure trace of the guiding-catheter. Then the pressure-wire sensor was advanced through the lesion to a distal position. 100microgram of nitroglycerine was administered to the guiding catheter to prevent arterial spasm. Maximal hyperemia was induced by intracoronary injection of 100 microgram of adenosine, and the aortic pressure at the guide tip (Pa) and distal coronary pressure (Pd) were simultaneously measured. FFR was calculated as the ratio of these pressures: Pd/Pa. At the end of FFR measurement the possibility of the drift of the trace was ruled out by pulling back the sensor to the tip of the guiding catheter.

- ### Data management with HCC

The complex cardiac database management software called Holistic Coronary Care (HCC) has been constructed using the Microsoft (MS) Access 2000 managing system as client software, handling two database files with different functions. The “HCC base.mdb” database file stores the measured data, while the “HCC.mde” file stores the forms, queries, macros and Visual Basic codes. The different results can be assessed and integrated via simple data entry with the use of contextual and graphical elements.

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- ### Statistical considerations

Predictive values were calculated. The positive predictive value of coronary occlusion for perfusion defect was calculated as the ratio of the number of segments with relative activity of <80% on the stress MIBI SPECT among the segments associated with a coronary occlusion (true positive): and this number plus the number of segments without perfusion abnormality within the region supplied by (sub)totally occluded coronary branch (false-positive). The negative predictive value was calculated as the ratio of the number of segments without perfusion defect on the MIBI SPECT (relative activity ≥80%) among the segments associated with a coronary branch without severe lesion (true negative) over all negative results, i.e. the previous plus the number of segments with normal MIBI activity in the region of an occluded coronary branch according to the coronary polar map (false-negative). The predictive values of coronary occlusion for wall motion abnormality were calculated by the same principle.

MedCalc software was used for statistical analysis when comparing the results of FFR and plaque volume. P-values less than 0.05 were considered statistically significant. Agreement between FFR and 3D angiography parameters was assessed using Pearson's correlation coefficient. The correlation between 3D parameters and FFR was assessed using linear regression analysis. Receiver operating characteristics (ROC) analysis was used to test the relationship between sensitivity and specificity at different cutoff values, and to establish the optimal 3D parameters cut-off value to predict an FFR <0.75. The correlation between 3D QCA segment length and the true wire segment length was calculated using Pearson's correlation coefficient.

# V. RADIATION MEASURES

For estimation of the radiation doses for SPECT, the IRCP effective dose was used. (48) Levels of ~ 6.7 and 5.8 mSv (11-13 mSv) were calculated for examinations at rest and exercise, respectively. ICA caused approximately 4-6 mSv during all examinations.

# VI. RESULTS

## 1. Integration of the result with HCC

### ○ ICA vs. SPECT

As a test of the accuracy of the generated polar map of coronary angiography and echocardiography, the overlap between the occlusion-associated regions derived by angiography and the corresponding defects observed on stress MIBI SPECT were evaluated, as were the resting echocardiographic segmental wall motion scores. The distributions of the segments with stress perfusion defects on MIBI SPECT gave positive and negative predictive values of coronary occlusion of 0.94 and 0.8, respectively.

### ○ ICA vs. echocardiography

According to the 16-segment wall motion analysis by echocardiography, the positive and negative predictive values for coronary occlusion for wall motion abnormality were 0.82 and 0.76, respectively.

## 2. 3D reconstruction vs. FFR

Regression analysis demonstrated a significant relationship between the cross-sectional area percentage stenosis (AS) calculated based on the 3D measurement and the FFR (r=-0.566, p= 0.008), and between the 3D derived plaque volume (PV) and the FFR (r=-0.501, p=0.018). On the other hand, the diameter stenosis (DS) and the minimal lumen diameter (MLD) did not correlate with the FFR values. The correlation between the 3D derived minimal lumen area (MLA) and the FFR did not reach significant level.

According to the Receiver Operating Characteristic (ROC) analysis the rank of the areas under the ROC curves (AUC) were the following:

1. PV (0.76), 2. AS (0.74), 3. DS (0.62), 4. MLA (0.55), 5. MLD (0.51).

The difference between the AUC of the PV and MLA was found to be significant (p=0.02). The best agreement with the FFR was found when the PV was >44% (sensitivity: 66.67 %, specificity: 82.35) and the 3D AS was 60% (sensitivity: 100%, specificity: 47 %).

## VII. DISCUSSION

It is always a multi-step process when ischemia detection takes place in patients with possible coronary artery disease. The goal is to decide whether conservative therapy or PCI is required. In recent years numerous studies have investigated the effects of applying combined non-invasive methods. When ICA is decided upon, the question might still arise whether the patient would benefit from intervention or not. COURAGE, a recently published multi-center trial comparing optimal medical therapy (OMT) versus PCI in stable CAD patients having at least one significant coronary artery disease with symptoms or at least one vessel with > 70% stenosis and evidence of ischemia by non-invasive testing (ECG, MPI or dobutamine-stress echocardiography), or stenosis > 80% with classic angina, showed that the survival after app. 5 years for the two groups were the same. Free-from-symptoms were fewer in the PCI group, and more than 30% of OMT group was shifted later to PCI group. This study had a heavy impact on the issue of „when-to-stent”, indicating that, even for significant lesions, intervention might not be superior to OMT.

Determination of lesion associated regions on a polar map corresponding to the coronary angiogram can only be determined with 3D reconstruction. With the limitations of the 2D reconstruction, multiple views provide satisfactory information concerning the coronary tree. With anatomical hallmarks, coronary lesions can be localized, and the affected artery and left ventricular segments can be paired on a polar map. With these associated data from the polar map and the coronary tree, the area-at-risk can be predicted. By pairing the anatomical and functional information, more precise definition of the disease can be obtained.

In the first part of our investigation, we measured the overlap between the anatomical and physiological area at risk to evaluate the fusion process. Recently, few efforts have been made to use the 17-segment model, but since it has not become widespread enough, we have decided to stick to the 16-segment one. Should the 17-segment model become the standard, the HCC software can be updated.

In our approach, first we calculated the predictive values of coronary anatomy detected by angiography for functional consequences measured by the non-invasive investigations. The generated polar maps of the coronary artery tree were compared with the detected 99Tc-labeled MIBI perfusion maps in order to test the accuracy of the new localizing method. The overlap between the predicted segments associated with the coronary lesion derived from the angiogram and the perfusion defects was analyzed in 10 postmyocardial infarction patients with subtotal or total coronary occlusion, lesions which would definitely cause perfusion defects during stress tests. On maximal vasodilatation in response to pharmaceutical or ergometric stress, the collateral circulation may be considered to be exhausted, as manifested by the well-established horizontal steal phenomenon. On the other hand, the distal part of the affected region always exhibits a higher degree of perfusion abnormality than that for the proximal part, which gives rise to the possibility that the better-collateralized proximal part of a lesion-associated region displays near-normal perfusion even under exercise conditions. In our analysis the well-developed collateral capacity could theoretically result in a false-positive prediction of a detected perfusion defect, especially in the basal segments, but the high positive predictive value of 0.94 for the perfusion abnormality proved that in clinical practice this potential error does not play a significant role.

With regards to the lower negative predictive value, it can be explained by a recanalized coronary lesion, providing good perfusion in the affected segments. However, the clinical data of our patients were not consistent with such a scenario, and we therefore think that the reason for false-negative results might have been due to attenuation artifacts or misalignment of the different imaging techniques.

The comparison of the results of coronary angiography with those of resting echocardiography in the same polar map furnished a lower predictive value of detected coronary lesions for wall motion abnormalities than for perfusion defects of SPECT, which can be explained by the collaterals providing enough blood-supply to make the segments move without visible disturbance at rest. In these cases, only the SPECT study revealed a stress perfusion defect, while our analysis yielded a “false-positive” result. On the other hand, a resting wall motion abnormality in a region supplied by coronary artery without a significant lesion was obviously due to remodeling of the entire left ventricle. This finding was not rare in our series of patients after extensive myocardial infarction and could result in a “false-negative” prediction of a wall motion abnormality, which might explain the relatively low negative predictive value.

When it comes to deciding to perform ICA, the significance of the lesion is not always obvious. QCA is a precise tool for calculating diameter and area, but it only uses the information from the 2D “picture” projection, with a good chance of showing the most severe luminal decrease. FFR measurement is considered as gold-standard and the most objective way of characterizing the flow decrease after the stenosis. During pharmacologically induced hyperemia, the ratio of the pressures distal and proximal to the stenosis is equal to the ratio of the maximal myocardial blood flow distal to a stenotic artery to the maximal flow in the absence of the stenosis. It also means that if we measure an FFR value of 0.75, the flow limitation is 25% of the normal flow during exercise condition; i.e. 25% increase can be achieved in the flow by successful intervention. In the DEFER and FAME studies, FFR-guided coronary intervention was found to be superior to 2D angiographically driven coronary intervention in preventing major cardiac events, validating the information from previous studies reporting only a modest correlation with FFR in 2D-QCA. Even few studies compared 3D-QCA and FFR on intermediate coronary stenosis. Saad et al. reported better accuracy of 3D-QCA than 2D-QCA in predicting FFR <0.75, finding a significant correlation between FFR and AS in 3D-QCA. Compared with FFR, the 3D-AS of 57% had the highest sensitivity and specificity for determining the significance of the lesion. Yong et al. compared the calculated parameters of 3D and 2D-QCA, and MLA correlated best with FFR and 3D-QCA showed a non-significant trend towards more accurate prediction of FFR than 2D-QCA.

Given that the 3D analysis of a coronary stenosis can provide more precise data determining the pressure drop, 3D approach can be a more accurate predictor of functional significance than 2D-QCA. In our study we found that AS >60% in 3D was one of the most important parameter. In our cases plaque volume > 44% of the target volume also proved to be a strong predictor of FFR <0.75. The latter finding is in line with the mentioned relation of the viscous friction pressure loss coefficient determined by the stenosis length in the Poisseuille’s law, because the plaque volume is also associated with the lesion length.

It is also possible to measure the plaque volume with intravascular ultrasound (IVUS), making it comparable with FFR. 3D-QCA only calculates the volume “inside” the lumen, whereas the same parameters calculated with IVUS give a greater value, since the latter also takes the “out-of-the-lumen” plaque part, i.e. the positively remodeled parts. Coronary CT angiography (CCTA) is also capable of detecting the plaque volume in the vessel wall. Kristensen et al found significant correlations between FFR and plaque volume and burden by CCTA in 56 coronary artery stenoses of 42 patients, proving that length was also a strong determinant of an abnormal FFR. (55) With CCTA both “in-the-lumen” and total plaque volume can be measured. They used the same method for calculations which we did: vessel area - lumen area/vessel area.

These results are in line with our opinion of the 3D-QCA PV, namely that it is an important 3D parameter, which should be taken into account for the assessment of the functional consequence of a coronary lesion. This parameter may even be considered a prognostic factor.

## VIII. SUMMARY/CLINICAL RELEVANCE

The moment a patient comes into an outpatient clinic, a cascade of investigations commences, which eventually may lead to PCI. After taking the previous history and risk stratification for ischemic heart disease, the patient usually proceeds to one or the other non-invasive imaging method. It often happens that the symptoms and risk stratification do not exactly match with the findings from the examinations. Acceptance of the clinical accuracy of the coronary artery polar maps leads to defining disease more accurately. Adequate localization of a coronary artery lesion within a given coronary circulation type is necessary for finding the association between the lesion and the affected segment. Careful evaluation can clarify the indication for intervention (both PCI or surgical). The method also permits a facile recognition of attenuation artifacts of the breast and the diaphragm during SPECT examinations, which can be a confusing factor in the evaluation. The regional wall motion polar map derived from the 2D echocardiograms by the use of a 16-segment model offers a simple and easily reproducible reference for the evaluation of the consequences of coronary disease with regards to resting wall motion abnormalities. Comparison of the wall motion data from routine echocardiography with the coronary angiographic and perfusion scintigraphy results in the same polar map provides detailed information about the state of the coronary disease. The absence of a resting regional wall motion abnormality in the left ventricular region of a significantly stenosed coronary branch means that there is no resting ischemia or a prolonged disturbance of the myocardial function. In this situation, we can carry on to stress MPI to reveal any (reversible) defects. When a resting wall motion abnormality can be detected in a region supplied by a severely stenosed coronary artery, an irreversibly (infarction) or reversibly (hibernation) damaged myocardium is present and further differentiation is required by viability studies. The same contraction pattern can be observed in the dysfunctioning segments due to remodeling when supplied by an intact branch. The clinical consequence of this finding is not revascularization, of course, but medical therapy. (60) We can conclude, that evaluating the results together on polar map gives an integrated approach, which helps to achieve a direct comparison of the supplying anatomy of the epicardial artery, the tissue perfusion and metabolism as well as the segmental contractile function.

When the decision is made to carry on for ICA, the possibility of finding an intermediate lesion arises. By QCA it is possible to give a good accurate with regards to the luminal changes, both diameter and area. Taking into consideration that the image we chose might not show the biggest luminal decrease, we can proceed to pressure-wire measurements, calculating the FFR, as the gold-standard for decision making prior to intervention. This requires special wires, but won't prolong the length of the procedure significantly. By "non-invasively" measuring the plaque volume, it is possible to decide upon the intervention at the controlling device. In our investigations we have concluded that measurements with 3D reconstruction correlated remarkably well with those of the FFR.

3D coronary reconstruction provides useful parameters on intermediate coronary lesions. Besides the 3D cross sectional stenosis, the calculated "functional" plaque volume characterizing the entire lesion is also an important predictor of the flow consequence of the stenosis.

In our project we conclude the following as new results:

- With the software HCC designed by us we are able to integrate the coronary tree from ICA onto a polar map, thus able to foresee the area-at-risk segments coupled to the diseased coronary segment. The information gained can be now compared to the results from echocardiography and SPECT as gold-standards with good predictive value, thus employing a new technique for making the decision on whether PCI is needed or not.
- Only a few studies have investigated the volumetric characteristics of coronary plaques, but none has made any comparison of 3D reconstruction parameters with FFR, previously only with data gained from 2D reconstruction. We have compared three 3D and two 2D plaque parameters with the FFR values, and found that PV and AS showed good correlation,

thus providing a new method for decision making with regards to the need of PCI when pressure-wire cannot be applied.

- In both parts of the investigation we have tested new methods with the hope of finding new tools for ruling out significant coronary stenosis, thriving to make all efforts to avoid false results, thus providing the patients with the best care they need.

# IX. Limitation

The number of subjects in both studies was relatively small, but the statistical analysis proved to be significant in our results. A larger scale study is needed to assess the clinical importance of 3D coronary angiography parameters. ICA and SPECT utilize ionizing components-radiation measures should always be kept in mind when referring patients to these methods, especially when young females are under examination.

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Candidate: Rudolf Kolozsvári

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## List of publications related to the dissertation

1. **Kolozsvári, R.**, Tar, B., Lugosi, P., Sánta, J., Béres, Z., Ungvári, T., Polgár, P., Kőszegi, Z.: Plaque volume derived from three-dimensional reconstruction of coronary angiography predicts the fractional flow reserve.
   *Int. J. Cardiol. Epub ahead of print (2011)*
   DOI: http://dx.doi.org/10.1016/j.ijcard.2011.04.010
   IF:3.469 (2009)

2. Kőszegi, Z., Balkay, L., Galuska, L., Varga, J., Hegedűs, I., Fülöp, T., Balogh, E., Jenei, C., Szabó, G., **Kolozsvári, R.**, Rácz, I., Édes, I.: Holistic polar map for integrated evaluation of cardiac imaging results.
   *Comput. Med. Imaging Graph. 31* (7), 577-586, 2007.
   DOI: http://dx.doi.org/10.1016/j.compmedimag.2007.06.008
   IF:0.848

## List of other publications

3. Steinbeck, G., Seidl, K., Brachmann, J., Hoffmann, E., Wojciechowski, D., Kornacewicz-Jach, Z., Sredniawa, B., Lupkovics, G., Hofgärtner, F., Lubinski, A., Rosenqvist, M., Habets, A., Wegscheider, K., Senges, J., Andresen, D., Édes, I., **Kolozsvári, R.**, The IRIS Investigators: Defibrillator implantation early after myocardial infarction.
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5. Kőszegi, Z., Balkay, L., Galuska, L., Varga, J., Hegedűs, I., Fülöp, T., Balogh, E., Jenei, C., Szabó, G., **Kolozsvári, R.**, Rácz, I., Édes, I.: Holistic polar map for integrated evaluation of cardiac imaging results.
*Comput. Med. Imag. Grap. 31* (7), 577-586, 2007.
DOI: http://dx.doi.org/10.1016/j.compmedimag.2007.06.008
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6. Kőszegi, Z., **Kolozsvári, R.**, Varga, J., Galuska, L., Szűk, T., Csapó, K., Fülöp, T., Hegedűs, I., Apró, D., Vaszily, M., Péterffy, Á., Édes, I.: 99mTc-MIBI SPECT assessment of the effects of aneurysm resection on the left ventricular morphology.
*Acta Cardiol. 59* (5), 541-546, 2004.
IF:0.532

The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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## Grants/Awards

- **Young Investigators Conference 2000, University of Debrecen, 26th place**: Assesment of the Result of Aneurysm Resection on Left Ventricular Morphology and Functional Changes by Imaging Techniques
- **Annual Congress of Hungarian Cardiologists, Youth Section, 2001, 1st place**: Haemodynamic Monitoring by Impedance Cardiography During Exercise Test
- **Hungarian Science and Technology Foundation, Project Prepairing Grant, Bilateral Research Comettee of Hungary and USA, 2002**: Expanding Diagnostic Possibilities in Ischemic Heart Disease
- **Annual Congress of Hungarian Cardiologists, Youth Section, 2003, Award of Lilly Hungary Ltd.**: Zero Distal Embolisation During Stent Implantation Into Coronary Bypass Venous Grafts