Ph.D. thesis

INTEGRATED EVALUATION OF CARDIOLOGICAL IMAGING TECHNIQUES

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Introduction

The atherosclerotic coronary heart disease is the primary cause of morbidity and mortality in the civilised word.

Beside the rest and exercise ECG, the non-invasive and invasive imaging techniques play important role in the diagnosis of the ischemic heart disease. Among the non-invasive investigations the most frequently used techniques are the echocardiography and the planar or tomographic scintigraphy (single photon emission tomography: SPECT). Furthermore, the positron emission tomography (PET) also has been available in Hungary for the recent years. For the patients requiring interventions beyond the medical treatment, the invasive investigation is unavoidable for the anatomical assessment of the coronary arteries.

In the diagnosis of coronary heart disease the non-invasive imaging techniques represent great importance not only because they more sensitive and specific than the exercise ECG in the detection of significant coronary stenosis, but they precisely indicate the functional consequences of the coronary lesions. Exercise perfusion scintigraphy and dobutamine echocardiography are competitive techniques for the assessment of coronary heart diseases.

SPECT creates a three-dimensional (3D) image of the concentration of the labeled molecules. After the injection of a perfusion labeling tracer like ^{99m}technetium-metoxy-isobutyle-isonitryle (^{99m}Tc-MIBI) or ^{201}thallium-cloride (^{201}TlCl) the myocardial distribution of the isotope is proportional with the perfusion and can be detected by the SPECT camera rotating around the heart. For clinical interpretation standard reorientation is the routine evaluation technique on the reconstructed images in 3D. Different axes are used for creating slices: perpendicular to the anatomical axis of the heart (resulting the short axis slices) vertical long axis and horizontal long axis.

The polar map or bull's eye display is often used for mapping the heart in nuclear imaging. In this portrayal scheme the entire left ventricle is displayed, the apex located to the middle of the map while left is the septal, right is the lateral, up is the anterior and down is the inferior direction.

The cationic thallium-201 has similar properties to the potassium. The distribution of this isotope in the myocardium according to blood flow. Redistribution of thallium is seen if serial imaging are performed after the injection of the tracer. Fill-in of an ischemic defect is due to more rapid washout from normal segments and slower washout from ischemic segments.

The technetium labeled MIBI binds to the mitochondium by intracellular metabolic processes. The advantage of technetium over thallium is the higher photon energy yields better image quality. Exercise tests can be carried out with both isotopes enabling us to search regional ischemia due to inadequate coronary reserve. The rest and the exercise images have to compare for this purpose.

According to the principle of positron emission tomography (PET) biologically active tracer molecules labeled with positron emitting isotopes can be detected by the PET camera. After the annihilation of the positron, the emitted two high-energy (511keV) gamma photons are registered by a coincident detector. The data are stored in the memory of a computer and reconstructed in 3D and to a two-dimensional (2D) distribution map by dedicated software.

For tracing the carbon hydrate substrate utilization of myocardium the positron emitting ^{18}F-deoxyglucose (^{18}FDG) have been developed.

This tracer is uptaken by the metabolically active cells and intracellularly phosphorilated by the hexokinase. Because the FDG-6-phosphate is not a substrate for the next enzyme, it is trapped intracellularly. The rate of the accumulation is proportional to the metabolic activity of the cell.

Echocardiography is the most common non-invasive imaging technique of the heart. Ultrasound waves are created and detected by pieso-electric crystals.

The reflected waves can be detected in different methods. In the *M-mode technique* one crystal acts as both transmitter and receiver. The wave travels through the body and bounces back from the different type of tissues having unique acoustic densities. Measuring the time for the signal to be reflected back allows the computer to calculate and display the region of interest. In the *2D echocardiography* the multiple M-mode beams are fired to create a real-time playing mode of the heart. Doppler-mode gains advantage of the Doppler’s law. The transducer detects the frequency shift. This kind of measuring gives data about the blood flow velocity relations in the heart.

Coronary angiography is widely used invasive investigation with minimal risk in the hand of a trained cardiologist. It clearly demonstrates the presence of a narrowing of a coronary artery caused most frequently by atherosclerotic plaques. The integration of the information of separated non-invasive and invasive investigation is not yet fully accomplished. Problems are arising both from the co-registration of different 2D and 3D imaging techniques and from the fitting the anatomical and functional data. However, integrated (holistic) approach is crucial for the correct settlement of the diagnostic and in the therapeutic algorithm of patients with coronary heart disease.

The perfusion abnormality caused coronary lesions can be reversed by percutaneous coronary intervention or bypass surgery resulting better life quality and quantity for the patient. Presently only the coronary angiography is the only method to show the possible coronary intervention. However the indication of an intervention is based not merely on the anatomical picture imaged by the angiogram but rather the functional consequences detected by the tissue perfusion and metabolic investigations.

Aims

A/ Elaboration of the theoretical and practical basis of the integrated evaluation of cardiological imaging techniques (echocardiography, roentgen ventriculography, SPECT, PET, coronary angiography)

A/1: comparison of roentgen ventriculography, planar scintigraphy and PET results

A/2: 3D co-registration of coronary angiogram with 3D scintigraphy and 2D echocardiography for integrated evaluation

B. Cardio PET/SPECT investigation in the clinical practice

B/1: determination of myocardial viability for predicting the outcome of revascularisation

B/2: planning the resection line before the resection of left ventricular aneurysm and assessing the morphological and functional result after the operation

III. Methods

III/1

SPECT and planar scintigraphy

For SPECT imaging 400-600 MBq technetium-99m labeled-MIBI was injected intravenously in the resting position and during the peak exercise.

Image acquisition was started 60-90 min later an APEX HELIX dual-headed gamma camera (Elscint) in single-head mode. 60 images were acquired in 64*64 matrices (pixel size: 6.9

mm) on a 180° arc from RAO 45° to LPO 45°, using a high-resolution collimator; the image acquisition time was set to 25 sec.

Images were evaluated with a dedicated quantitative myocardial perfusion program package (ACSP-2, Elscint). After 2D filtering with a Butterworth filter (parameters: 0.35 and 5), reconstruction was performed, 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. Quantitative polar maps were generated from both the preoperative and the postoperative images. From the polar map the average activities of 16 regions were expressed as percentages of the highest one.

For planar scintigraphy data aquistion was gathered from three projections (AP, LAO 45° and 70°). Quantitaive circumferential profil evaluation was calculated by DIAG (Mediso) software packadge.

III/2

PET

Data aquisition was carried out with GE 4096 Plus whole body scanner after oral glucose loading in static way 40 min after the injection of glucose analoge 18FDG. Emission images were corrected for photon attenuation by a 20 min transmission scan obtained using Germanium 68 external ring source. 15 contigous transaxial slices were reconstructed with 5 mm in plane resolution.

The perfusion/metabolism studies were performed with a whole-body positron emission tomograph (model 931-08/12, CTI Siemens in Leuven and GE 4096 Plus in Debrecen) provided with eight detector rings permitting simultaneous acquisition of 15 planes, with an interplane spacing of 6,75 mm. A small cyclotron (cyclone 10/5, Ion Beam Application) and auxilary chemical processing equipment were used to produce ^{18}FDG and $^{13}NH_3$. Before each study, a 2-minute rectilinear scan was used for positioning the heart within the field of view and a 15-minute transaxial transmission scan with a 68Ge ring source for photon attenuation correction was performed.

The myocardial perfusion studsies were performed in Leuven using $^{13}NH_3$ ammonia: 20 mCi of $^{13}NH_3$ dissolved in 5 ml saline was slowly infused followed by a flush of 20 ml saline. Acquisition was started simultaneously with the injection of $^{13}NH_3$. 19 dynamic frames were recorded (12x10 sec, 4x30 sec, 3x2 min).

Regional myocardial utilisation of exogenous glucose was evaluated with ^{18}FDG. The metabolic studies were performed with a euglycemic hyperinsulinemic clamp technique or after oral glucose loading. The tracer dose of 10 mCi was injected not earlier than 50 minutes after $^{13}NH_3$ injection to allow isotope decay, 3x10 min frames were summed and evaluated in a static way.

The last 2 frames (reconstructed using a Hanning filter with a cutoff frequency of 0.3 units) of the perfusion examinations were analysed. The long axis of the left ventricle was indicated manually from two views and 5 short axis slices were generated with equal distance along the long axis with automated delineation of the myocardium by ECAT (Siemens) software. Relative activities were determined for the averaged activity value of a segment by comparing the activity to normally perfused myocardium within the image. Regions were defined as PET viable when the relative flow activity was higher than 0.8 ("normal") or when the ratio between metabolic and flow activity was higher than 1.2 ("mismatch").

III/3

Echocardiography

All patients had an echocardiographic examination with a Sequoa eguipment, using a 3.5 Mhz harmonic imaging transducer, the end-systolic and diastolic left ventricular diameteres were measured, and the ejection fraction was calculated by Simphson rule. Wall motion abnormalities were evaluated using the 16 segments model. Using the Doppler Myocardial Imaging technique the early diastolic velocity (E), the late-diastolic velocity (A), the ratio of early and late-diastolic velocities (E/A) was calculated. In the systolic phase the isovolumic contraction velocity (IVC - if it was well differentiated), the systolic velocity (S) and the late-systolic velocity (LS – if it was present) were also measured.

III/4

Coronary and left ventricular angiography

Cardiac catheterisation was performed by the Judkins technique. Coronary arteriograms were recorded in multiple projections. Left ventriculography was performed in the 30° right anterior oblique view by injecting 30-40 ml contrast medium. Films were exposed at a rate of 25 frames/sec. The boundaries of end diastolic and end systolic left ventricular silhouettes were traced automatically. Coronary angiograms were evaluated by two experienced invasive cardiologists who were blinded to the PET results. Coronary artery segments were identified and categorised according to the accepted standards. The percent reduction of the internal luminal diameter in the projection with maximal severity was assessed visually. The patency of the diseased vessels was scored according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. The retrograde filling was scaled similarly to the grading system described by Rentrop et al: 0, no visible collaterals, 1: retrograde filling of side branches without visualisation of the epicardial segment, 2: partial retrograde filling of epicardial segments and 3: complete retrograde filling of epicardial segments. Only cases evaluated in agreement were involved.

III/5

3D co-registration of coronary angiography for integrated evaluation with scintigraphic and echocardiographic data

III/5/ a: Coronary polar map

For comparison of the coronary artery tree to the polar map basically two projections were taken into consideration: the 30° right anterior oblique (RAO) and the 45° left anterior oblique (LAO) views. These projections were selected because they are approximately parallel to the atrioventricular and interventricular grooves, the two main plains of the heart. The epicardial coronary arteries are running in these grooves according to the "circle and loop" rule. This means that the LAD and the posterior descending of the RCA or the LCx complementary occupy the anterior and posterior interventricular grooves (loop) while the LCx and the RCA (usually its inferorolateral branch) share the atrioventricular groove (circle). Therefore, the two projections are appropriate to estimate the anatomical distribution of coronary circulation. This allows localization of the coronary branches and their lesions to a local co-ordinate system (polar map) of the heart as usually applied for nuclear imaging. From the RAO projections the LAD/RCA border was assessed comparing the left and right coronary angiograms. The termination of visually detected end-arteries showed the separation of myocardial beds supplied by the two branches. The border of the myocardial beds on the polar map was determined on the "vertical axis" of the local co-ordinate system taking into account the proportion of separation. The RCA/LCx separation can be determined from the LAO view. In this projection the left ventricular septal edge was delineated by the LAD, and the LCx showed the lateral epicardial surface. The border between the RCA and LCx territory could be assessed quite sharply by comparing the left and right coronary angiograms from the same view. The origin of the first marginal branch from the LCx representing the separation of LAD/ LCx beds could be detected from this projection, too. The border of anterior and posterior septal myocardial beds supplied by the septal branches of LAD and the posterior descending branch (usually) of the RCA was hypothesised as a line superimposed on the "horizontal axis" of the polar map. The localisation of side branch territories was also possible on the polar map by careful analysis of running of the individual branches. The position of the lesions was determined in relation to side branches' hallmarks.

The "lesion predicted region" (LPR) was defined as the myocardial bed of a diseased artery distal to the lesion.

III/5/b:

The 16 echokardiographic segments on the polar map

A special report from the American Heart Association, American College of Cardiology, and Society of Nuclear Medicine defined standards for plane selection and display orientation for serial myocardial slices generated by cardiac 2D or tomographic 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, the two most widely used cardiac imaging modalities, 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 patient management involving cardiac perfusion and function.The names for the 90°-oriented cardiac planes used in all imaging modalities should be *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 this16-segment scoring system analyzed in blinded fashion without knowledge of patient identity.

Evaluation of the segmental wall motion uses 1-5 scores, 1: normokinesia, 2: hypokinesia, 3 akinesia, 4: dykinesia and 5: aneurysm. For summarizing the results for the entire left ventricle, the 16 segments can be projected for the left ventricle polar map by the same principles as for the nuclear studies. In the local coordinate system of the heart, from the ("reoriented") 2 and 4 chamber long axis views the 6-6 examined segments take place along the vertical and the horizontal axis of the polar map. Together with the results of the remaining 4 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 to the polar map. This polar map is a rotated version of the scheme which was originally proposed by Feigenbaum. He summarized the 16 left ventricular segments in a map, but his aim had not involved the comparison of the results with nuclear imaging techniques. The newly developed portrayal map is appropriate for integrated analysis of different images. For the registration of different techniques to the same polar map, the anatomical hallmarks like the apex, the long axes, the papillar muscles, and the junction of the right ventricle can be used. This 16-segment echocardiographic polar map is more easily comparable to the polar map generated from the tomographic images if the average of the activities in the same 16 segments are calculated from the scintigraphy. Evaluating the results together with the coronary polar map this integrated approach has achieved a direct comparison of the supplying anatomy of the epicardial artery, the tissue perfusion and metabolism as well as the segmental contractile function.

III/6:

Statistical analysis

Values are expressed as a mean ± SD. A paired t-test was used for intra-group comparisons. For comparisons between two groups an unpaired t-test was applied. Differences were considered significant at $p < 0.05$. The sensitivity, specificity, positive and negative predictive value were calculated in the usual way.

IV.: Results

IV/1:

Comparison of X-ray left ventricular angiography, planar scintigraphy and ^{18}FDG-PET results

Comparing quantitatively the metabolic imaging with ^{18}FDG-PET in relation to rest planar Tl-201 flow scintigraphy in akinetic regions identified by roentgen ventriculography 5 patients with pervious myocardial infarction were investigated. One-one segment from every projection (LAO-45°, AP, LAO-75°) of Tl-scintigraphy (each divided to 5 segments) was rendered to the 5 myocardial segments visualized from RAO-45° view by contrast cineventriculography. Metabolism-perfusion mismatch (relative ^{18}FDG activity > 1,2x relative Tl activity) was detected in 20 segments (51,3%). Our results support that the ^{18}FDG-PET proves significantly more potentially reversible myocardial damages than the planar Tl-scintigraphy either defining the viability by 50% preserved metabolic activity or metabolism-perfusion mismatch.

^{99m}Tc-MIBI SPECT, ^{18}FDG-PET studies and DTI results

In order to assess the myocardial viability ^{99m}Tc-MIBI SPECT flow investigations were compared with the metabolic ^{18}FDG-PET studies. In the hibernated segments (where the relative metabolic: flow activity ratio > 1.2) a very accentuated systolic velocity can be observed in the beginning of systole, in that phase, where the QRS complex of ECG can be registered and just before the appearance of the first heart sound on simultaneously recorded phonocardiography, so it is suggested to be the isovolumic contraction. The relatively low systolic velocity is also characteristic in hibernated segments.

IV/2:

3D co-registration of coronary angiography for integrated evaluation with scintigraphic and echocardiographic data

Localising the coronary distribution on the polar map

Using the borders of the three main myocardial beds we found the usual right dominant variation of the coronary circulation with the usual length of the LAD in 12 pts (66.7%). In the case where the LAD ran far over the apex the "long LAD" term was used while if the posterior descending supplied a considerable part of the apical bed the "short LAD" terminology was used. In one third of the cases there was a different type of coronary pattern including super right dominant (11.1%), long LAD or short LAD (5.6-5.6%) and left dominant (11.1%) circulation.

Lesion predicted region (LPR) asssessment

In order to test the lesion predicted localising method we evaluated 10 patients with a single severe lesion. The corresponding defects on $^{13}NH_3$ perfusion polar maps were compared to the mentally generated polar map of coronary angiography. The overlap of the real $^{13}NH_3$ defects and the LPR-s were assessed. According to the distribution of the overall 330 segments the sensitivity, the specificity, the positive predictive value (PPV) and the negative predictive value (NPV) were found to be 0.82, 0.94, 0.94 and 0.81, respectively

Regional tissue perfusion and metabolism in relation to epicardial flow and prediction of viability by angiography

To indicate the total segmental epicardial flow, we summed the anterograde TIMI flow grade and the retrograde collateral grade in every LPR segment. A summed score of 0-2 indicated poor epicardial flow (group A) while 3 or more points represented maintained epicardial filling (either anterograde or retrograde) (group B). Regarding the tissue perfusion assessed by the relative $^{13}NH_3$ activity in relation to the summed epicardial flow we found significantly higher mean $^{13}NH_3$ activity in group B as compared to group A: 65.4±17%, and 45.6±10% respectively ($p=0.001$). A similar difference was detected in the metabolic activity where 47.4±11% relative ^{18}FDG activity was found in group A vs. 68.6%±16 in group B ($p=0.0004$). There was no significant intragroup difference between the averages of $^{13}NH_3$ and ^{18}FDG activities within both groups ($p=0.12$ and 0.13). However, with a cutoff value of 3 for summed epicardial flow, the positive predictive value of angiographically detectable good epicardial filling for PET viability criteria (ie. $^{13}NH_3$ activity ≥ 80% or/and metabolic flow rate > 1.2) was only 0.50, while NPV was calculated as to be 0.82

As a test the power of the mentally generated polar map of coronary angiography and echo-cardiography, the overlap between the occlusion-associated regions derived by angiography and the corresponding defects on MIBI SPECT, and also the echocardiographic segmental wall motion scores were evaluated. The distribution of the total of 160 segments with rest perfusion defects on MIBI SPECT and the wall motion abnormalities detected by echocardiogaphy gave positive and negative predictive values of coronary occlusion of 0.94 and 0.81 against SPECT, and 0.82 and 0.76 against echocardiography, respectively. Further analysis revealed that the relative MIBI activities of the individual segments correlated significantly with the wall motion scores ($r = -0.87$).

In an other 10 patients set data from echocardiography, coronary angiography and SPECT/PET in 16 left ventricular segments were compared in a polar map display. All patients had previous myocardial infarction (mean age: 50.1±12.2 years, EF: 34.1±12.7%). The segments showing wall motion abnormality with less than 50% ^{18}FDG activity were regarded as infarcted (scarred) regions. The cases with more than 50% relative ^{18}FDG activity in the dysfunctioning regions, and with more than 70% diameter stenosis in the supplying epicardiac coronary arteries, were defined as hibernating myocardium. Dysfunction caused by remodelling was considered if coronary angiography did not reveal significant coronary artery stenosis in the supplying epicardial artery. The incidence of perfusion-metabolic mismatches in the segments was examined by comparing the ^{99m}Tc-MIBI SPECT with the ^{18}FDG-PET results. The data revealed 48 (46.6%) dysfunctioning segments with low metabolic activity (infarction-I). In 29 (28.2%) segments with significant coronary stenosis on the supplying coronary artery, the metabolic activity was maintained (hibernation-H). In 26 (25,2%) segments, the hypo- or akinesia was associated with (nearly) normal epicardial coronary branch (remodelling-R).

A significant correlation (r=0.77, p=0.01) was found between the incidencies of R and I segments. No correlation was noted for the incidences of the H and I segments (r=0.11, p=0.76). The presence of perfusion-metabolic mismatch was detected only in 45% of the H regions (13/29). The results show that 1. remodelling is more frequent after large myocardial infarction, 2. mismatch pattern can be demonstrated only in a part of hibernating myocardium.

IV/3:

Prediction of the result of high-risk coronary bypass surgery by positron emission tomography

Coronary angiography revealed three-vessel disease in a 56-year-old male with two previous myocardial infarctions. Coronary bypass surgery was initially ruled out by cardiac surgeon because of the poor left ventricular function (EF: 23%), despite moderate viability signs during conventional isotope techniques. Positron emission tomography with 18FDG indicated a large periinfarction area of hibernating myocardium. Accordingly, coronary bypass grafting was performed. Postoperatively, the symptoms disappeared, the left ventricular wall motion abnormalities (with the exception of the scarred region demonstrated by PET) improved, and the global left ventricular function increased significantly.

IV/4:

^{99m}Tc-MIBI SPECT assessment of the effects of aneurysm resection on the left ventricular morphology and function

Pre- and postoperative rest ^{99m}Tc-MIBI SPECT images were analyzed in order to characterize the features of left ventricular aneurysms (LVA) and the changes in the 3D scintigraphic parameters after apical LVA resection in 6 patients. In the middle horizontal slice an angle was defined to quantify the apical divergence associated with the LVA. After the resection, the changes in the divergence angles (DA) were measured as were the changes in the left ventricular volumes (LVV) by volumetric calculations using ellipses superimposed onto horizontal and vertical long axis slices of the left ventricle.

The mean DA decreased from an average of 38.5°±11.32° preoperatively to 24°±11.84° postoperatively ($p=0.03$). The mean LVV also decreased significantly: from 476.7 ± 107.6 ml to 335.0 ± 93.2 ml ($p=0.01$).

As regards the severity of the perfusion defect in the LVA segments, the resectable LVAs were associated with a very low isotope uptake (<20% relative activity). A DA >20° was also characteristic of anatomical LVA in all patients.

The significant decreases of DA and LVV after resection reflect favorable morphological changes in the left ventricle (reverse remodeling). We consider ^{99m}Tc-MIBI SPECT a useful method for LVA detection; it can also furnish good guidance in the planning of the resection line. Tomographic perfusion allows an analysis of the morphological (and indirectly the functional) results of the surgery.

Beyond the morphological improvement in one case the perfusion also improved after the aneurysm resection. Left ventricular aneurysm had detected at the 55-year-old woman after extensive anterior myocardial infarction in association with progressive ventricular dilatation and symptoms of heart failure. Coronary angiogram revealed a serious lesion in the proximal segment of the left anterior descending coronary branch with a poor run off tract. ^{18}FDG-PET and ^{99m}Tc-MIBI-SPECT investigation were performed on order to differentiate the scarred regions from the viable myocardial segments. Taking into consideration the results an aneurysm resection was performed without revascularisation procedure. After the surgery not only the ejection fraction and the left ventricular dilatation had improved but the tissue perfusion in the segments surrounding the resected aneurysm had also showed a significant increase at the follow up MIBI-SPECT imaging.

V.: Discussion

The variations in coronary anatomy are always to be considered when one associates a myocardial region to a supplying coronary artery. The exact in vivo determination of a myocardial perfusion area of a particular coronary artery theoretically requires the three dimensional (3D) registration of both the coronary artery system and the imaged left ventricle to the same coordinate system. This has not been achieved for the time being despite sophisticated algorithms were reported for assessing the 3D structure of coronary tree. Usually the angiography report serves as the only reference for evaluation of myocardial scintigraphies as the functional consequence of coronary artery abnormalities.

The usual coronary artery distribution is often indicated on the polar map by referring to the three main coronary branches' territories. Nevertheless the individual variations may differ very much from the most common one. Right predominant circulation was reported with about 60-70% frequency, but this classification system pays attention only to the distribution between the RCA and LCx branch and does not incorporate variations in distribution between the RCA and LAD as frequently occurs at the free walls of ventricles and apical region. In our series of patients we found a common coronary distribution in two thirds of cases while in one third different pattern was observed.

To assess the 3D coronary artery structure and to determine the myocardial territory associated with a coronary lesion we developed a method integrating different projections of the coronary artery tree. Using anatomical rules and assumptions of the epicardial surface (id. the shape of the left ventricle), the 3D characteristics of the coronary artery anatomy could be translated in a (two-dimensional) polar map display. This bull's eye portrayal scheme was chosen because it has been used widespreadly for the mapping of the heart in nuclear imaging. Furthermore the diagnostic usefulness of this displaying of 3D radiotracer distribution has been validated.

The generated polar maps of the coronary artery tree were compared with "real" $^{13}NH_3$ perfusion maps in order to test the accuracy of our lesion predicted region (LPR) method for localising perfusion abnormalities. The overlap between the LPR segments derived from the angiogram and the perfusion defects (<80% relative $^{13}NH_3$ activity) detected by PET was analysed in the ten patients who showed a single severe lesion. The high PPV of 94% has validated the approach. The somewhat lower NPV of 81% may reflect the fact that in certain cases even a >85% stenosis could be "compensated" by coronary autoregulation maintaining normal rest perfusion. This is in line with several recent studies which reported near normal rest perfusion even in exclusively collateral dependent regions of occluded coronary branches.

In our series of patients we found a significantly higher $^{13}NH_3$ perfusion activity in segments with good epicardial filling (group B) than in the territories with limited anterograde and/or retrograde epicardial flow (group A). Regarding the metabolic activities the same tendency was observed. There was no significant intragroup difference between the average of $^{13}NH_3$ and ^{18}FDG activities. However, further segmental analysis of the data of these patients revealed that good epicardial flow detected by angiography does not necessarily indicate viable segments according to PET criteria of relatively maintained perfusion or mismatch. The PPV has been found to be as low as 50%. On the other hand the NPV was considerably higher (81%). Interpreting these results we have to conclude that the epicardial blood supply in one part of the patients was not associated with nutritive tissue perfusion which is consistent with other studies reporting the evidence of ”no reflow” phenomenon.

The TIMI flow grade in acute myocardial infarction and prognosis were studied in relation to clinical outcome by Lenderink et all. They concluded that patients with TIMI grade 2 flow at discharge had mortality rates similar to those with TIMI flow grades 0 and 1, while prognosis was better in patients with TIMI flow grade 3. Although our patient population represents a rather chronic situation, our results are in line with their findings because the high negative predictive value of epicardial filling for viability may explain the wrong prognosis of patients with TIMI flow grade less than 3. Regarding the low positive predictive value of epicardial flow, we can speculate that despite the prognosis being generally better in the patients with TIMI flow 3, there may be a subgroup of these patients with less viable myocardium. These patients can not be separated by angiography alone and there is no published data about their prognosis. Other factors are also to be taken into consideration like effects by mechanisms other than salvage of ischemic myocardium and preservation of left ventricular function. In this sense, the advantages of an open artery include more than the myocardial salvage alone. The retrograde epicardial flow must play a similar role in the benefits but one can hypothesise that the presence of collaterals do not necessarily implicate nutritive tissue flow for preservation of myocardial viability.

This concept is consistent with the dynamic and time-related development of collateral flow that occurs after advanced coronary stenosis or occlusion and may explain, at least in part, the different conclusions on the importance of collaterals drawn from the different time of point of investigations after the infarction. There is no doubt that pre-existing collaterals at the onset of myocardial infarction are associated with limitation of infarct size and may prevent left ventricular aneurysm formation. On the other hand this concept emphasizes the possibility of postnecrotic collateral developement in the segments without viable tissue.

In the hibernated segments, where chronic ischemia is present, chracteristec DMI pattern was detected. Both the systolic and diastolic velocities were decreased, but a high isovolumic contraction velocity could be detected. According a possible explanation, the hibernated myocardial cells have specific transformation. The normal adult-specific myocardial proteins (troponin) are destroyed, and foetal proteins appears in the cells (i.e.: titin, etc). It suggests, that this foetal contarctile proteins have different peculiarities, than the adult, and type of the contraction is significantly different in these segments, than in normal ones. The abnormal contraction pattern is followed by an abnormal relaxation, that is why the diastolic velocities also changes. Alternative explanations for the high isovolumic contraction velocity arise as a "frustrain contraction" or because of the "thretenig effect".

VI.: Summary

In this thesis various results of the subspecialisated cardilogy were attempted to resyntetized in order to serve a "holistic" approach of the coronary heart disease. A method was proposed for generating coronary artery polar maps in order to predict lesion associated territories. In this way direct comparison of the angiogram with non-invasive imaging techniques (echocardiography, SPECT, PET) can be obtained for the evaluation of functional consequences of coronary artery disease.

The results of the 2D investigations (echocardiography and coronary angiogram) were semiquantitatively co-registered with real 3D scintigraphic techniques (SPECT, PET) and displayed in a polar map scheme providing useful predictions about the functional outcome of a possible intervention.

The integrated polar map interpretation of the 16 left ventricular segments (originally derived from the echocardiography) makes it possible to correlate between different functional data and epicardial coronary anatomy. This segmental comparison differentiates

1. the ischaemic regions with normal resting perfusion and contarction associeted to a culprit coronary lesion,
2. the disfunctioning but viable (hibernating) segments supplied by diseased coronary branch,
3. the disfunctioning segmentes due to remodelling supplied by intact coronary branch,
4. the irreversible damaged (scarred) region which is not worth to revascularise but may be resectable in case of aneurysm formation.

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