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

The impact of three-dimensional coronary reconstruction in the planning of stent implantation and in refining the intracoronary physiological measurements

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1. Introduction

1.1. In-stent restenosis

Over the last three decades, stent implantation became the most widely performed procedure for the treatment of symptomatic coronary artery disease. Despite the new drug eluting devices, in-stent restenosis (ISR) remained the leading cause of late stent failure. The incidence of ISR depends on the clinical characteristics of the patient and may reach 5%. The risk factors can be divided into systemic (e.g. diabetes mellitus), procedural (e.g. underexpansion of the stent) and local vessel determinants. Regarding local features, the design, the length and the diameter of the stent were shown to be independent predictors of ISR. The vascular tortuosity was also proven to be an important factor.

Lesions located in severely angulated coronary artery segments have been associated with an increased risk for major adverse cardiac events after stent implantation. The mechanism behind this phenomenon was proposed to be the change of the wall shear stress, as a contributor of intimal hyperplasia. However, the question ”whether the detected intimal hyperplasia is a part of the healing process after stent implantation or a predictor of later clinical restenosis” has not yet been answered.

Conventional two-dimensional (2D) coronary angiography may limit the characterisation of the actual impact of coronary vessel tortuosity. Instead, three-dimensional (3D) reconstruction is required to adequately recognise the anatomy and spatial run of the curved segment in question. Despite the specific software packages on the market with 3D reconstruction algorithm allowing an accurate geometric analysis of the tortuous coronary artery, the literature contains limited data about the impact of 3D coronary artery geometry on ISR, and conclusive data are lacking regarding the detailed effect of stent implantation on the 3D geometric changes.

The purpose of this study was to explore potential links between the data of the 3D analysis and late stent failure.

1.2. Fractional flow reserve (FFR) and non-hyperemic pressure ratio (NHPR) measurements

According to current guidelines, the physiological measurement of coronary artery stenoses is recommended in chronic coronary syndrome. Nowadays, FFR is considered to be a standard method for the evaluation of myocardial ischemia and the likely advantage of revascularization.

FFR is calculated as the ratio of distal coronary artery pressure (Pd) and aortic pressure (Pa) during maximal hyperemia, usually induced by intracoronary or intravenous adenosine.

The accuracy of physiological intracoronary measurements is influenced by several factors. Pitfalls may originate from the preparation (calibration, equalization) or from the measurement itself (submaximal hyperemia, drifting, whipping, wedging). In addition, the role of hydrostatic pressure influenced by the position of the pressure wire sensor in relation to the orifice is usually ignored.

Non-hyperemic pressure ratios (NHPR) are measured at resting phase, without the induction of hyperemia. The distal-to-aortic pressure ratio at rest (resting Pd/Pa) and the instantaneous wave-free ratio (iFR) are the most important non-hyperemic parameters, their popularity results from the lack of need for adenosine. Prior clinical trials (DEFINE-FLAIR, IFR SWEDEHEART) had proven that the iFR method (pressure ratio measured in a diastolic time of minimum myocardial resistance) has a similar ability to guide coronary revascularization as FFR. Previously, a close correlation between iFR and resting Pd/Pa (average distal-to-proximal pressure ratio at rest) had been shown. The resting Pd/Pa value of 0.92 was defined as cut-off.

1.3. Computed Tomography versus invasive angiography

In recent years, studies investigating the effect of hydrostatic pressure on intracoronary indices have been published. Most of these examinations were performed using computed tomography (CT) angiographies to calculate the height differences between the orifice and the different segments of the coronary arteries. Recently, an invasive angiography-based study has also highlighted the importance of height difference during pressure measurements at the highest and lowest sensor positions, potentially influencing FFR, iFR and Pd/Pa values. This study has challenged the concept of a single cut-off value for every coronary vessel.

Our aim was to investigate the effect of resting Pd/Pa and FFR adjustment based on the calculation of hydrostatic pressure gradient between the coronary orifice and the pressure wire sensor, to identify the relevance of hydrostatic pressure during clinical decision making, particularly in cases where FFR values were near the cut-off (between 0.7 and 0.9). We also aimed at specifying the effect of hydrostatic pressure in different segments of the coronary artery system.

2. Methods

2.1. Study design and patient population

At first part of the investigation, in this retrospective, multicentre study, we screened patients referred for a repeat coronary angiography 3-30 months following stent implantation. Cardiac catheterisations were performed in the haemodynamic laboratory of the Department of Cardiology and Cardiac Surgery, University of Debrecen and Jósa András Teaching Hospital, Nyíregyháza between 1st January and 31st December 2015. All data were retrospectively analysed from the hospital information system and from the local PACS database.

The main inclusion criteria were the presence of an implanted stent with a length ≥18 mm and the availability of at least two different angiographic images recorded from the target coronary artery segment ≥25° apart. Patients either with bare-metal (BMS) or drug-eluting stents (DES) were included. The stent platform was restricted to that of cobalt-chromium, which assured a quite homogeneous group regarding the mechanical characteristics of the stent. Patients, in whom the stent was implanted in a coronary artery bypass graft were excluded, as well as cases with poor image quality or unsuitable images for 3D reconstruction. Altogether 64 patients fulfilled all criteria (mean age: 65±9 years).

The second part of the investigation was designed as a single center retrospective experiment to verify height differences between the coronary orifice and the pressure sensor, thereby exploring the impact of hydrostatic pressure. 2 and 3D analyses were performed based on two and three-dimensional methods in patients undergoing intracoronary pressure measurements in the haemodynamic laboratory of Department of Cardiology, Jósa András Teaching Hospital, Nyíregyháza for the assessment of intermediate coronary stenoses (50-90% diameter stenosis) from December 2016 to May 2019.

We performed 3D reconstruction of 41 coronary lesions of 37 patients to assess the height difference between the catheter tip and the intracoronary pressure sensor. We used this value to calculate the effect of the hydrostatic pressure on the measured resting Pd/Pa and on the FFR. By this method, we were able to perform hydrostatic pressure calculations, even in lack of a lateral projection. In the next step, we investigated the correlation between the 3D height calculations and the 2D measurements carried out from the lateral view. Further, we measured the height difference between the catheter tip and preferably all 10 segments predefined using the Syntax segmentation of the 37 patients from the lateral views of the coronary angiographies in 2D. Limited by the quality of the lateral views to determine the heights between the tip of the catheter and the most distal point of the segment in question, we performed 305 measurements in 2D.

The study complies with the Declaration of Helsinki; data were analyzed anonymously (44270/2013/OTIG).

2.2. Intracoronary pressure measurement

All catheterizations were performed using the radial approach. Following unfractionated heparin (5000 IU) administration, the pressure wire (PressureWire™ X Guidewire, Abbott) was positioned at the tip of the 6F guiding-catheter. Next, nitrate was administered and the pressures were equalized at the tip of the catheter. Then, the wire was advanced distally to the stenosis by 2-3 cm. FFR measurement was performed during hyperemia induced by intracoronary bolus of 200 µg adenosine. Pressure curves were recorded continuously until the hyperemic effect completely eliminated, and pressures reverted back to the resting Pd/Pa ratio. At the end of the procedure, the pressure sensor was pulled-back to the tip of the catheter to exclude any pressure drift.

2.3. 3D reconstruction

A dedicated software package (QAngio® XA 3D Research Edition 1.0 program, Medis Specials bv, Leiden, The Netherlands) was used for 3D coronary artery reconstruction from two angiographic views (at least with 25° difference). First, the program was calibrated (mm/pixel), then the appropriate frames were selected. After designating the proximal and distal endpoints of the coronary segment to be examined, the program provides the centerline of the vessel course and then the contour of the vessel wall.

Finally, the program creates a rotatable 3D coronary artery model, and we obtain the data characterizing the segment under intervention and its edge parts. The amount of time needed to perform 3D analysis is approximately 3-4 minutes.

2.4. Curvature analysis based on 3d reconstruction

Quantifications of the ACr and the bending angles of the proximal and distal edges of the target segment before and after stenting were performed both at end-diastole and end-systole. The appropriate frames were selected on the basis of the ECG traces. The arc was the midline of the analysed segment, while the chord was the distance between the proximal and distal edges of the analysed segment. To measure the bending angles at the edges of the target segment, we used two vectors along the centreline of the vessel towards the principal directions, 5-5 mm proximally and distally. The bending angle was defined as the angle of the two vectors subtracted from 180°. Both angles were measured during systole and diastole using images before ("pre-stent") and after stenting ("post-stent").

2.5. Height difference measurement in 3D

After the 3D reconstruction, the coronary model was rotated to a lateral projection (LAO 90°, CAUD 0°). From this view, the height appeared without any foreshortening. The final model included the length of the coronary artery segment, the arc-chord ratio and the foreshortening of the actual view. Following the correction of the chord length with the degree of foreshortening, a right triangle with a chord as hypotenuse was created. Within this triangle, the cosines of angle at the distal part multiplied by the length of the chord resulted in the height difference between the orifice and the pressure wire sensor.

2.6. Height difference measurement in 2D

For 2D height detection, the quantitation software of the X-ray system was used on angiographic recordings acquired in the lateral view, where the height difference between the orifice and the sensor is projected without any foreshortening. In the patient's supine position, the sternum is located on the left side of the screen, thus height differences are to be measured horizontally.

2.7. Coronary segmentation defined by the Syntax nomenclature

A modified version of the coronary segmentation defined by the Syntax scoring system was used in our study. This reproducible, schematic mapping of the coronary tree also accounting for the individual type of coronary circulation, creates an opportunity to determine the average height difference assigned to each coronary segment.

In our present study, 10 epicardial coronary segments were evaluated. The left anterior descending artery (LAD) was divided into a proximal, a mid and a distal segment. The end-point of the proximal circumflex artery (CX) was defined at the origin of the obtuse marginal (OM) branch, while the distal CX corresponded to the distal run-off of the vessel. The main right coronary artery (RCA) was also divided into a proximal, a mid and a distal segment, while the posterolateral (PL) and posterior descending (PD) branches were evaluated separately. The end- points of the PL and PD branches were defined at the levels where the luminal diameter became less than 2 mm. Since coronary pressure measurements are generally not performed in the left main stem (LM; stenoses of the LM are usually analyzed by positioning the sensor in the proximal LAD or CX) or in small branches with a diameter less than 2 mm, these segments were not examined in our study. A feasible place of the pressure wire sensor was determined at the distal end-point of each coronary artery segment.

2.8. Statistical analysis

All analyses were performed using the SPSS 20.0 for Windows (Statistical Product and Service Solutions, version 20, SPSS Inc., Chicago, IL, USA) and Medcalc 12.2.1.0. program. Normality was assessed with normal probability (Q–Q) plot and with non-parametric Shapiro-Wilk test. All variables following normal distribution were compared using Student t-test; for values not following normal distribution, the median and the interquartile range were expressed and compared between the groups using the Mann–Whitney U test. Continuous variables were reported as means with standard deviation (SD), while categorical variables were reported as numbers and percentages. Chi-squared test was performed for comparison of categorical variables.

At first part of the investigation univariate logistic regression analysis was performed to determine factors associating with ISR, and then multivariate logistic regression (forward stepwise, likelihood ratio test) was used to identify independent predictors of restenosis. Sex, diabetes mellitus, hypercholesterolaemia, smoking, nephropathy, hypertension and previous myocardial infarction were included in the analyses, together with the angiographic parameters of the proximal and distal pre- and post-stent bending angels, arc-chord ratios, as well as their changes. In the case of ACr, a convenient unit increase (1%) was used for the calculation of the odds ratio (OR) and its 95% confidence interval (CI). A linear regression model was used for analysing the relationship between each parameter. The cut-off value was determined with ROC analysis.

At second part of the investigation clinical characteristics were analyzed per patient, lesion characteristics and pressure data per lesion. The relation between 2D and 3D height difference measurements were assessed using a correlation analysis.

As an index of statistical significance, a p value <0.05 was accepted.

3. Results

3.1. Patient and lesion characteristics in the examination of curvature change

At first part of the investigation during the selected one year, 110 patients with repeat coronary angiography 3-30 months after stent implantation were screened. Sixty-four patients fulfilled all inclusion and exclusion criteria. DES was implanted in 37 patients, while BMS was used in 27 patients. In our study cohort, 22 patients were diagnosed with ISR, while 42 patients without any restenosis served as control. The two groups did not differ regarding major cardiovascular risk factors, proportion of the treated vessel or the type of stent. However, age was higher in the ISR group.

3.2. Results of coronary artery curvature analysis using 3D method

The assessments for the ACr and the bending angles were performed in both systole and diastole. There was no statistical difference in the average angles between the ISR and control groups. However, the pre-stent ACr was significantly higher in the ISR group (1.06 [IQR 1.03, 1.12] vs. 1.05 [IQR 1.03, 1.07], p=0.04). Moreover, the change in ACr after stenting was also higher in the ISR group (-0.02 [IQR -0.04, -0.01] vs. -0.01 [IQR -0.03, 0], p=0.03).

3.3. Correlation between pre-stent values of 3D parameters and their change due to stenting

Similar changes of the curvature have been observed with both stent types. The higher initial ACr values associated with more pronounced straightening of the curvature (DES: $r=-0.83$, $p<0.001$; BMS: $r=-0.86$, $p<0.001$). Significant negative correlations were also shown for the proximal and distal edge bending angles ($r=-0.7727$, $p<0.00$; $r=-0.7190$, $p<0.001$, respectively).

3.4. Changes in bending angles at the edges of the stented segment

Low (<7°) pre-stent edge bending angles often showed an increase after stent implantation, which can be explained by the newly generated buckling tendency at the edges of the stent in case of the straightening of the initially curved stented segment. On the other hand, the high initial values of the bending angle at the edges of the target segment associated with decreasing bending angles, presumably due to the slight overspreading of the stent's longitudinal straightening effect beyond its edges.

3.5. Logistic regression analysis for in-stent restenosis

The univariate logistic regression analysis demonstrated that the pre-stent ACr and the percentile change in ACr after stenting correlated with the ISR. However, the multivariate logistic regression modelling showed that only the pre-stent ACr was an independent predictor of ISR (odds ratio for 1% increase of the ACr: 1.08; $p=0.012$).

The ROC analysis indicated a possible cut-off value at 1.055 for pre-stent ACr to predict ISR (AUC=0.61; sensitivity=59%, specificity=60%).

3.6. Patient and lesion characteristics in the examination of hydrostatic pressure

At second part of the investigation during the examination period 147 FFR measurements were performed simultaneously with resting Pd/Pa detection in patients with a percent diameter stenosis between 50 and 90. In case of 57 lesions, FFR values were between 0.7 and 0.9. Sixteen cases were excluded due to incomplete hyperemia (caused by suboptimal cannulation of the orifice or developing a significant pause during the administration of adenosine), lack of a lateral DICOM view, poor image quality or images unsuitable for 3D reconstruction. Overall, 37 patients with 41 lesions were enrolled. The distribution of the lesions was the following: 3 proximal, 18 mid and 6 distal LAD, 1 proximal and 5 distal CX, 2 mid and 6 distal RCA. Hypertension, diabetes, dyslipidemia, age, body weight, height, body surface area (BSA, calculated from body weight and height), left ventricular end-diastolic diameter (LVEDD) and ejection fraction (EF) were examined, these data are presented in Table 1. Procedural results of the invasive physiological assessment, attributes of the investigated vessels (in terms of minimum lumen diameter of the interrogated lesion (MLD), percent diameter obstruction at MLD [%DS]), as well as resting Pd/Pa value and FFR value of the overall population are also presented in the table below.

Patient and lesion characteristics in the examination of hydrostatic pressure

Patient characteristics	**All patients n=37 (mean±SD)**	**Female n=16 (mean±SD)**	**Male n=21 (mean±SD)**	**p value**
Age	66.65±6.22	68.06±6.27	65.91±6.74	0.3740
Weight (kg)	85.85±16.47	77.73±11.88	91.93±15.28	**0.0205****
Height (cm)	169.37±6.75	163.40±4.85	173.85±6.75	**0.0002**
BSA (m2)	2.00±0.22	1.87±0.14	2.10±0.19	**0.0044****
LVEDD (mm)	55.36±6.94	52.00±6.40	57.76±6.54	0.0504
EF (%)	50.89±11.90	55.53±12.69	47.57±10.97	0.1136
Hypertension	35(95.6%)	16 (100%)	19 (90.5%)	0.5923**
Diabetes	15(40.5%)	6 (37.5%)	9 (42.9%)	0.7603**
Dyslipidaemia	17(45.9%)	9 (56.3%)	8 (38.1%)	0.4444**
MLD (mm)	1.37±0.34	1.34±0.32	1.39±0.35	0.7185
%DS	52.95±6.28	53.13±6.68	52.81±5.97	0.9093
Resting Pd/Pa	0.90±0.04	0.91±0.05	0.89±0.05	0.4498
FFR	0.83±0.04	0.84±0.03	0.82±0.03	0.0765

BSA: body surface area; EF: ejection fraction; FFR: fractional flow reserve; LVEDD: left ventricular end-diastolic diameter; MLD: minimum lumen diameter of the interrogated lesion; Resting Pd/Pa: distal-to-aortic pressure ratio at rest; SD: standard deviation; %DS: percent diameter obstruction at MLD

**Mann-Whitney test was performed on continuous variables showing non-normal distribution.*

***Chi-squared test was performed on categorical variables.*

3.7. 3D reconstruction-based analysis of the coronary tree

The start point of the proximal LAD was usually located at a similar height as the left orifice. Overall, the LAD took an upward course with its highest point detectable at the left ventricular apex (distal LAD) in supine position. The overall CX ran in a downward course. The RCA took an upward course first, then the mid segment ran horizontally, and finally, in case of a right dominant coronary circulation, the distal RCA took a downward course and bifurcated into the PD and PL branches. The PD branch went towards the apex taking a slight upward course, while the direction of the PL branch was similar to that of the distal RCA.

3.8. Correlation between 3D and 2D height differences between the catheter tip and the pressure wire sensor

A 3D reconstruction rotated into the lateral projection was applied in order to determine the degree of height difference. The 2D Quantitative Coronary Analysis (QCA) software of the local catheterization laboratory (Syngo Angio; Siemens) was used for simple distance measurements with an automated calibration from the lateral view (LAO 90°, CAUD 0°). We found a close correlation between the two methods ($r=0.9805$, $p<0.0001$.

3.9. Analysis of height difference between the catheter tip and different coronary artery segments based on the Syntax segmentation

The circulation type of the coronary anatomy was defined by assessing the 2D left and right coronary angiograms. This approach was used to provide a more accurate description of the 10 investigated coronary segments, compared to the Syntax score system. Three hundred and five measurements were performed using 2D lateral projections. The most distal point of the segment was compared to the tip of the catheter. In case of the LAD, every segment was located higher than the orifice (proximal LAD: –13.69±5.4 mm; mid LAD: –46.13±6.1 mm; distal LAD: –56.80±7.7 mm), and the highest point of the vessel was at the apex. The studied segments of the CX were located lower than the orifice (proximal CX: 14.98±8.3 mm; distal CX: 28.04±6.3 mm), while height differences measured for the RCA were least prominent (proximal RCA: –6.39±2.9 mm; mid RCA: –6.86±7.0 mm; distal RCA: 17.95±6.6 mm). All studied PL and PD branches originated from the RCA, their height differences were 29.65±6.1 and 17.53±6.6 mm, respectively.

3.10. Effect of hydrostatic pressure on FFR and resting Pd/Pa values per different coronary artery segments

The hydrostatic pressure decreased the cut-off value of 0.80 FFR in the mid and distal LAD, while there was an apparent increase in the distal CX.
In our study population (41 lesions with FFR measurements between 0.7 and 0.9), the correction for height differences changed the interpretation of the measurement in 5 (12%) and 11 (27%) cases for the FFR (cut-off value at 0.80) and the resting Pd/Pa (cut-off value at 0.92) measurements, respectively.

3.11. Effect of body structure on height difference

Body structure influences the size of the heart, which corresponds to the distance between the coronary orifice and the coronary artery segments. The body weight, body height and therefore the body surface area (BSA) significantly affected the height differences measured between the coronary orifices and some epicardial segments. In our study, the body weight demonstrated a stronger correlation with the distances between the coronary orifices and the coronary artery segments than the body height, especially in case of the RCA. The impact of BSA was similar to that of the body weight.
The LVEDD measured by 2D echocardiography showed a significant correlation with the distance between both the left coronary orifice and the proximal and mid LAD, and the right coronary orifice and the mid RCA.

4. Discussion

At present, the exact mechanism of restenosis is not fully described. It is well known that stent implantation has an effect on the geometry of the coronary artery, but data regarding the impact of coronary angulation on restenosis is limited and controversial. Previous studies demonstrated that macroscopically, the stent placement induces straightening of the arterial segment. In animal model the rigid stent implantation increased the edge curvature of the stented segment by 121% and 100%. In human investigation the straightening effect of the stent implantation was identified as a predictor of restenosis. However, Fukuda later concluded that the lesion angulation was not associated with restenosis following early generation sirolimus-eluted stent implantation. Recently, Gomez-Lara et al. examined the role of bendings, vessel curvature and angulation in target vessel revascularisation with the comparison of two second-generation DES platforms. The authors demonstrated that the angulation of the lesion or the changes of the vessel angulation from pre to post-implantation did not correlate with target vessel revascularisation and target lesion failure at 1 year follow-up. On the contrary, the restriction of the hinge motion after stent implantation was reported as a predictor of restenosis.

It is important to notice that the above mentioned clinical studies used 2D analysis to determine vessel angulation and geometric changes. It is also known that overlapping and foreshortening are main limitations of the 2D QCA assessment. These factors make an accurate spatial coronary reconstruction very difficult, which makes the determination of coronary curvature inaccurate.

A recent investigation emphasised the advantages of 3D QCA by demonstrating that the stent implantation changes the natural tortuous course of coronary arteries, and the decrease in the coronary bending angle contributes to stent failure. The authors described coronary curvatures by measuring the maximum and mean bending angles at different time points. They showed that the mean systolic post-stent bending angle and the change in the mean systolic bending angle after stenting may be predictors of restenosis. In that study the maximum and mean bending angles were chosen to describe the target segment’s bending angles. In our opinion it may be difficult to standardise the determination of the maximum or even the mean bending angle across a severely tortuous segment. Therefore we decided to use the ACr, which provides a more reliable characterisation of a tortuous coronary segment, even if it contains multiple curvatures.

At the moment, it is unclear how the geometric change following stent implantation provokes restenosis development, and what the exact pathomechanism of restenosis could be. Given that the endothelium is able to produce anti-atherogenic substances (e.g. nitrogen monoxide and endothelin) in response to shear stress, it is generally accepted that one of the main contributors of stenosis development in native coronary arteries is the presence of a pathologically low shear stress. Also, several precise computational fluid dynamics models described that vessel bending changes have significant effect on local haemodynamics resulting in altered endothelial shear stress. However, the role of shear stress in stenosis development after stent implantation is more ambiguous. Based on available data, a recent review rose the question whether intimal hyperplasia is part of the healing process after stent implantation or a predictor of later clinical restenosis. It is reasonable to analyze not only the flow parameters but also the stress and strain in the vessel wall generated by the radial stretching effect of the implanted stent. As for the magnitude of these forces, the normal value of the average wall shear stress in a coronary artery is considered approximately 1 Pa only, while the stretching effect of an implanted stent could generate even $3x10^5$ times higher circumferential stress.

In line with previous literature data, we demonstrated that the curvature of the target coronary artery segment significantly decreased after stenting due to the straightening effect of the stent. In contrast to some previous studies, our results did not support the idea that the straightening effect of the stent always generates an increase of the angles at the edges of the stent. In particular, we observed an increase after stenting in cases of pre-stent edge bending angles <7°. In these cases, the straightening of the stented coronary artery segment generated a buckling tendency at the edges of the stent, which was in line with previous observations. On the other hand, bending angels generally decreased in cases of higher initial values due to the longitudinal straightening effect spreading slightly over the edges of the stent.

In our study, the predictor of restenosis was the pre-stent ACr. If the pre-stent ACr was higher than 1.055, the risk of ISR increased. While the relatively low sensitivity and specificity of this cut-off value reflect the multifactorial nature of restenosis, our results may propose a new concept for stent positioning in a curved coronary artery segment.

In cases of high ACr, the development of restenosis could be explained by the increased wall stress. According to Hook's law, the force due to the bending of the stent will be proportionate to the initial ACr. In our hypothesis, the force due to the bending of the stent is one of the main source of the increased wall stress after stenting, which is as an important facilitator of abnormal intimal proliferation. Therefore, the clinical importance of appropriate stent length regarding ACr should be considered.

We can see, therefore, that the implementation of revascularization can only be done after very careful consideration.

According to Pascal´s law the hydrostatic pressure in the coronary arteries can be assumed as 0.77 mmHg per cm height difference, in case of a normal mass density (1050 kg/m3). Studies applying CT coronary angiography have previously showed that pressure differences are systematically detectable between the anterior and posterior coronary territories in supine position. Moreover, height measurements at the highest or lowest points of the individual vessels indicated remarkable differences. In a previous study, intracoronary pressure measurements (resting Pd/Pa and FFR) were carried out in both supine and prone positions, and height differences were analyzed based on CT images. These studies unequivocally found a significantly lower resting Pd/Pa and FFR values measured in the LAD, while higher values were demonstrated when measurements were carried out in the

CX or RCA.

Hydrostatic pressure calculated from height difference measurements is a constant parameter. The effect of this parameter depends on general pressure conditions, being more prominent at lower pressures. The direction of the effect depends on the orientation of the sensor compared to the coronary orifice. Higher sensor positions result in increasing, while lower positions decreasing FFR and Pd/Pa values. During routine invasive coronary angiography, the determination of height differences between the coronary orifice and the pressure sensor using 2D or 3D assessment enables the correction of FFR and resting Pd/Pa ratios, by subtracting the hydrostatic pressure from the measured distal pressure.

In our study, the effect of the calculated hydrostatic pressure difference for 10 epicardial coronary segments of the Syntax nomenclature were analyzed. We found a similar range of values as reported in prior studies, however, in the past, no specifications for the Syntax segmentation were available. For example, Harle et al. found a mean bias of FFR caused by hydrostatic pressure compared to a zero level of −0.048 in the LAD, 0.02 in the CX, and 0.02 in the RCA. In our study, these values were –0.011, –0.036 and –0.044 for the proximal, mid and distal segments of the LAD, respectively; while they were 0.012 and 0.022 for the proximal and distal CX, respectively. In case of the RCA, the average difference between the pressure ratios in the calculated and corrected values were –0.005 for the proximal and mid, and 0.004 for the distal RCA, respectively. The change in the pressure ratios after the correction for hydrostatic pressure were 0.023 and 0.014 for the PL and PD branches, respectively.

When evaluating an individual coronary circulation, the variations in coronary anatomy need to be considered. The Syntax epicardial segmentation incorporates the Laeman classification with two main coronary circulation types. However, it is known that the individual coronary anatomy may show further variations depending on the length of the LAD and the spatial distribution of the CX and RCA. Of note, all PL and PD branches originated from the RCA in our study population. In one of our previous papers, we suggested an extension of the Syntax classification to the 12 different coronary patterns. In our current study, we used a similar classification to interpret the results of the hydrostatic pressure measured in the individual coronary artery segments. It was our team which used this approach first evaluating the role of hydrostatic pressure individually for each coronary artery segment.

Given the dichotomous interpretation of stenosis severity by the FFR measurement, we found a similar rate in the change of classification of an intermediate severity coronary artery stenosis after adjusting for hydrostatic pressure as in previous publications. As a result of the correction of pressure ratios at 100 Hgmm aortic pressure, the interpretation of the measurements changed in 5 (12%) and 11 (27%) cases in our study population. This rate is in accordance with previous data (12.9%), and overall represents the potential clinical significance of hydrostatic pressure measurement.

As body weight (and consequently the BSA) significantly influenced the measured height differences between the coronary orifices and most of the epicardial segments, normalization for this parameter may also be necessary in the future to create a universal correction factor for hydrostatic pressure. To this end, larger scale studies are needed to establish a well-defined normalized correction factor for each coronary artery segment in all types of coronary circulation.

5. Summary

The use of curvature analysis performed on the basis of three-dimensional coronary artery reconstruction for planning stent implantation opened up new possibilities predicting in-stent restenosis. Pre-stent arc-chord ratio and bending angles at the end of the stent showed strong correlation with their changes during stent implantation. The arc-chord ratio defines the spatial curvature of the examined vessel segment well, furthermore it is possibly able to predict pathological proliferation of the intima caused by chronic stress in the coronary artery wall. The pre-stent ACR proved to be an independent predictor of in-stent restenosis, therefore taking into account the extent of this parameter during election the length and positioning of the stent – especially in focal lesions – can further improve the percutaneous coronary intervention.

Based on the results from clarification of intracoronary physiological measurements we can declare that in coronary stenoses located at distal segments with unclear significance, the clinical importance of hydrostatic pressure calculation could be pronounced. Direction of the alterations - caused by hydrostatic pressure - in fractional flow reserve and resting Pd/Pa values depend on the vertical orientation of the pressure wire sensor to the tip of the catheter at the coronary orifice. The effect of hydrostatic pressure correlates with the current aortic pressure inversely.

The values of hydrostatic pressure detected per segment were similar in different patients. This perception can be the first step to create an accurate correction factor for each

segment of coronary artery system, resulting the possibility of the segment based, empirical decision making.

Considering the rising of image-based pressure ratios (e.g. QFR), an invasively measured pressure corrected by hydrostatic values could clarify further the less-invasive algorithms, and improve the precision of these new assessments of coronary physiology.

Original observations of the doctoral thesis:

Based on the results of the doctoral thesis the following original statements are made:

- The pre-stent arc-chord ratio proved to be an independent predictor of the development of in-stent restenosis, however, based on sensitivity and specificity alone, it is not a clinically applicable parameter to predict in-stent restenosis.
- A change in the arch-chord ratio following stent implantation may be a possible cause of in-stent restenosis.
- Initially smaller edge angles were observed to increase after stenting, while larger ones were observed to decrease overall.
- Based on 3-dimensional coronary reconstruction performed using invasive angiographic imaging, the height difference between coronary segments can be calculated.
- Determination of height difference by 2D and 3D methods shows a close correlation with each other.
- Clinical significance of the calculation of hydrostatic pressure is especially pronounced in the case of coronary stenoses at the border of significance, its consideration is recommended especially in the case of pressure measurements in the distal coronary segments.
- Using Syntax score-based segmentation, the hydrostatic pressure difference specific to each coronary segment can be determined.

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7. Appendix

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Subject: PhD Publication List

Candidate: Áron Üveges
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Üveges, Á.**, Tar, B., Jenei, C., Czuriga, D., Papp, Z., Csanádi, Z., Kőszegi, Z.: The impact of hydrostatic pressure on the result of physiological measurements in various coronary segments.
   Int. J. Cardiovasc. Imaging. 37, 5-14, 2021.
   DOI: https://doi.org/10.1007/s10554-020-01971-w
   IF: 2.357 (2020)

2. **Üveges, Á.**, Jenei, C., Kiss, T., Szegedi, Z., Tar, B., Szabó, G. T., Czuriga, D., Kőszegi, Z.: Three-dimensional evaluation of the spatial morphology of stented coronary artery segments in relation to restenosis.
   Int. J. Cardiovasc. Imaging. 35 (10), 1755-1763, 2019.
   DOI: http://dx.doi.org/10.1007/s10554-019-01628-3
   IF: 1.969

List of other publications

3. Tar, B., Jenei, C., **Üveges, Á.**, Szabó, G. T., Ágoston, A., Dézsi, C. A., Komócsi, A., Czuriga, D., Juhász, A., Kőszegi, Z.: Hyperemic contrast velocity assessment improves accuracy of the image-based fractional flow reserve calculation.
   Cardiol. J. 28 (1), 163-165, 2021.
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   IF: 2.737 (2020)

4. Csippa, B., **Üveges, Á.**, Gyürki, D., Jenei, C., Tar, B., Bugarin-Horváth, B., Szabó, G. T., Komócsi, A., Paál, G., Kőszegi, Z.: Simplified coronary flow reserve calculations based on three-dimensional coronary reconstruction and intracoronary pressure data.
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5. Szabó, G. T., **Üveges, Á.**, Tar, B., Ágoston, A., Dorj, A., Jenei, C., Kolozsvári, R., Csippa, B., Czuriga, D., Kőszegi, Z.: The Holistic Coronary Physiology Display: calculation of the Flow Separation Index in Vessel-Specific Individual Flow Range during Fractional Flow Reserve Measurement Using 3D Coronary Reconstruction.
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Cardiol. Hung. 49 (6), 418-423, 2019.
DOI: http://dx.doi.org/10.26430/CHUNGARICA.2019.49.6.418

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