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

Functional and Physiological Cardiac Examinations in Chronic and Acute Coronary Diseases

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1. Introduction

1.1. Clinical forms of ischemic heart disease

Ischemic heart disease (IHD) and its complications are the leading causes of mortality worldwide in spite of highly developed preventive and therapeutic standards. According to the onset of complaints, IHD can be divided into two main diagnoses: chronic coronary syndrome (CCS) and acute coronary syndrome (ACS). Considering pathological findings as well as the repolarization signs on ECG, ACS has three main forms: acute myocardial infarction with ST elevation (STEMI), acute myocardial infarction without ST elevation (NSTEMI), and unstable angina, which does not cause definitive myocardial damage.

1.2. Time factors determining the outcome of acute coronary syndrome

In the outcome of ACS, an early diagnosis is important to reduce ischemic time. The prognosis of ACS is determined by different time factors, which are the qualitative features of the health care services and indicators of the health awareness level of the population as well. Hesitating time is calculated from the onset of typical acute symptoms and the contacting of the health care system, and it is independent from the organizational level of the health care system. The duration calculated from the time point of the first medical contact until hospital admission (door) represents prehospital healthcare and transport time. Door-to-balloon time represents the duration between hospital admission and the opening of the ACS-related coronary artery, and it is related to the organization of hospital workflows.

To establish the diagnosis, an ECG has to be performed, which is usually made before hospital admission. Several studies have proved that telemedicinal ECG with direct cardiological consultation improves the prognosis of this patient population.

1.3. Cardiogenic shock

Cardiogenic shock (CS) is the most serious complication of ACS and significantly increases mortality. The disease is characterized by hypotension and hypoperfusion affecting multiple organs. Making the diagnosis is the main goal in the case of CS. The diagnostic process of CS includes coronary angiography if it is a complication of ACS, and coronary revascularization is the curative solution.

1.3.1. Intra-aortic balloon pump counter pulsation

The use of mechanical circulatory support devices is part of standard CS treatment. Intra-aortic balloon pump counter pulsation (IABP) was part of the therapeutic protocol during our clinical study. IABP enhances myocardial perfusion and indirectly cardiac output via decreasing the afterload. Recent guidelines recommend IABP only in special cases, because this form of device support failed to improve mortality rates in CS patients in the IABP-SHOCK II (NCT00491036) clinical trial. This trial was heavily criticised, mainly because the extension of coronary lesions and the area at ischemic risk (AAR), as well as the changes in the myocardial perfusion after percutaneous coronary interventions (PCI), which were not taken into consideration when interpreting the study results.

1.3.2. Prognostic factors of cardiogenic shock

Age, hypoxic brain damage, reduced left ventricular (LV) pump function, and prehospital reanimation were previously proven as influencing factors of mortality in patients suffering ACS complicated with CS. To achieve further improvement in mortality rates, the identification of other predictors is required. Early diagnosis is of importance in CS; however, the role of telemedicine has not been explored in this population yet. Moreover, most of the studies do not assay the exact determination of the culprit artery and related AAR with supplied LV mass, and consequently their role is not transparent in the case of mortality either. As AAR in ACS is an independent predictor of mortality, it is likely to have an impact in CS, too.

1.4. The importance of three-dimensional coronary angiography

Coronary angiography is part of the examination process in both ACS and CCS. Two-dimensional (2D) coronary angiography is a widely used tool to explore the anatomical and pathological status of coronary arteries. Three-dimensional (3D) imaging can provide a more accurate description, which also supplies data for flow modelling, beside anatomical parameters.

1.5. Physiological examination of coronary arteries

Multiple lesions on the coronary tree can be observed as a frequent constellation. In certain cases, the ischemic relevance of a lesion is questionable if one estimates with non-invasive examination techniques only. Recent guidelines emphasize the role of coronary angiography extended with physiological examination for the determination of the severity of IHD and the indication of optimal therapy.

1.5.1. The physiologic relevance of coronary lesions

The atherosclerosis of the coronary arteries leads to IHD. Coronary plaques are forming in predilected localizations, where wall shear stress (WSS) caused by the blood flow enhances the remodelling of the arterial wall. WSS is proved to be an independent predictor in plaque progression in a clinical trial (PREDICTION, NCT01316159). Coronary stenoses lead to the alteration of flow character, a disturbed turbulent flow is appearing instead of a benign laminar flow, which eventuates locally a low and oscillating WSS. Endothelial dysfunction caused by altered coronary flow accelerates atherosclerosis via multiple inflammatory pathways.

1.5.2. Left ventricular territory related to coronary arteries

The extension of myocardial territory related to a coronary lesion is an important and independent prognostic parameter in the outcome of IHD, therefore, its calculation has additive value in therapeutic decision-making.

1.5.3. Fractional flow reserve

Randomized clinical trials in IHD have proven that fractional flow reserve (FFR) has a prognostic value. Current guidelines recommend its use to indicate a PCI in the case of intermediate stenosis, if the ischemia is not properly detected non-invasively in the related supplied territories. FFR is determined under maximal vasodilation with intracoronary (ic) administrated pharmacological challenge. Moreover, important data can be generated about the pressure gradients without hyperaemia.

1.5.4. Coronary flow reserve

Coronary flow reserve (CFR) is proved to be an independent predictor in IHD mortality. In spite of FFR, which mainly demonstrates the hemodynamic changes related to a lesion on epicardial level, CFR is indicative of the entire circulation related to the interrogated artery, including the microcirculation.

1.5.5. Simultaneous determination of fractional flow reserve and coronary flow reserve

FFR and CFR utilize different approaches for the description of coronary lesions, therefore their simultaneous determination enhances the value of functional investigation. The calculation of the indices originated from one examination is technically more favourable.

In the arteries without lesions laminar flow is detected, but parallel with the formation of the stenosis, turbulent flow becomes a significant contributor, alongside the development of flow separation. Laminar flow is directly proportional to the pressure drop related to friction; in contrast, flow separation has a quadratic link to the pressure gradient. Functional assessment derived from one examination method has to calculate with different flow characteristics, and showing the local importance of a lesion with its relevance to the entire artery, including the microvascular tract.

2. Aims

In our present research, we aimed to investigate the hospital mortality of patients with ACS complicated with CS, with regard to prehospital parameters as well as AAR and the myocardial perfusion of PCI.

We also aimed to develop and validate a hemodynamic calculation method to detect the functional significance of coronary lesions, which is based on the use of pressure data originated from FFR measurement and the 3D reconstruction of coronary angiography. Another goal was to describe the flow separation index (FS_i) in order to quantify the turbulent flow and compare its value with FFR and CFR.

3. Patients and methods

3.1. Patient population

All patients treated because of ACS complicated with CS between 1 January 2009 and 31 December 2012 in our department were enrolled into our study for the analysis of CS mortality predictors. Patients with mechanical complications at admission were excluded.

In the study, for the elaboration and validation of the coronary physiology calculation method, coronary angiography and FFR measurement data of 16 patients were used, if moderate stenosis was detected by the 3D quantitative coronary angiography on one epicardial vessel. Exclusion criteria were multivessel-IHD, ostial lesions, left main coronary artery involvement, acute indication for coronary angiography, or previous coronary bypass graft operation (CABG).

3.2. ECG consultation via telemedicinal route

In some ACS cases, transtelephonic ECG was performed by the ambulatory services and sent to our department for direct consultation. During the consultation, ECG evaluation, the alignment of the specific therapy, and the circumstances of patient transport were discussed.

3.3. Ischemic time intervals

Ischemic time intervals were calculated in the ACS population, including pain-to-door time as the duration between the onset of typical chest pain and hospital admission, as well as door-to-balloon time, defined as the time between hospital admission and the first balloon dilatation in the culprit coronary artery.

3.4. Heart ultrasound examination

In the ACS patient population, echocardiography was performed in all patients. By echocardiography the exclusion criteria were verified. In our study, LV ejection fraction (EF) was used among the parameters detected during the examination.

3.5. Coronary angiography, percutaneous coronary intervention

Invasive coronary angiography, and PCI were performed (if indicated) in both population groups. Imaging was made with standard fluoroscopic projection, and documented with 15 frame/s recording velocity. The strategy of PCI including the type of stent was left to the discretion of the interventionl cardiologist,

3.6. Three-dimensional coronary reconstruction

Two 2D images, in 25° angulated projections, were used for 3D coronary reconstruction. The interrogated arteries were analysed from their origin until the level of the pressure wire sensor area. Anatomy descriptive parameters were obtained from 3D coronary reconstruction.

3.7. Calculation of left ventricular supplied territory

In the ACS patient population, the supplied LV territories were determined regarding all 3 epicardial coronary arteries. AAR was defined as the supplied region of a culprit artery. Both calculations were performed with the use of Holistic Coronary Care (HCC) software.

3.8. Left ventricular perfusion examination

Changes in the myocardial perfusion among ACS patients were detected by the Quantitative Blush Evaluator (QuBE) software. According to all three main coronary arteries, perfusion in the supplied territories were determined. LV global perfusion value (LV QuBE) was obtained from these results. Perfusion value in the AAR (AAR QuBE) was also measured in all culprit arterial supplied territories, this value was divided by the segment number of AAR, defined the perfusion value related to one AAR segment (1 AAR segment QuBE).

3.9. Fractional flow reserve

In CCS patients, after coronary angiography, FFR measurement was performed. Pressure data during the resting phase were obtained after the administration of ic. glyceryl trinitrate. Maximal vasodilatation was achieved by ic. administration of 200 μg adenosine.

3.10. Coronary flow reserve

$CFR_{p\text{-}3D}$ was obtained from the data of 3D coronary reconstruction and intracoronary pressure data during the resting phase and maximal vasodilatation. In our calculation, the equation of volumetric flow and pressure drop (Δp) was used, as of

$$\Delta p = f * Q + s * Q^2.$$

Δp is derived from FFR measurement as the difference of aortic pressure (P_a) and the pressure distal to the stenosis (P_d). The linear friction coefficient (f) was calculated according to the Hagen-Poiseuille equation:

$$f = 8\pi\mu \frac{L}{A^2}$$

where μ-t was taken 3,5mPas, as the viscosity of the blood. The length of the interrogated segment (L) and its surface (A) were obtained from 3D coronary reconstruction. The separation coefficient (s) was characterized by the Borda-Carnot formula:

$$s = k_{sep} \frac{\rho}{0.266} \times \left(\frac{1}{MLA} - \frac{1}{A'_d} \right)^2$$

where an empiric correction factor (k_{sep}) was added to our calculation, because instead of the original formula, the calculation was based on the flow changes between the starting and outflow point of the segment. The density of the blood (ρ) was 1055 kg/m^3. The minimal lumen area (MLA) as well as the vessel surface at the outflow point of the interrogated segment (A'_d) were obtained from the 3D coronary reconstruction.

The equation describes the connection between pressure and volumetric flow (Q) as:

$$Q = \frac{-f + \sqrt{f^2 + 4s \times \Delta p}}{2s}$$

3.11. Flow separation index

The flow separation index (FS_i) is a dimensionless parameter, which reflects to the turbulent blood flow type. Its value is independent from the vessel diameter and from the absolute value of the volumetric flow. FS_i is calculated as a quadratic drop through a lesion in a coronary artery, according to the formula:

$$\mathrm{FSi} = \int_1^{CFR} \left(\frac{s * Q^2}{P_a}\right) d(Q_{act}/Q_{rest})$$

where Q values are obtained from parameters of actual (Q_{act}) and resting phase (Q_{rest}) measurements.

3.12. Statistical analysis

Normal distribution was identified with the Kolmogorov-Smirnov test in ACS data and with the Shapiro-Wilk test in CCS data. Normally distributed, parametric variables were tested with the Student t-test, the categorical variables were compared by Wilcoxon-Mann-Whitney test. Logistic regression analysis was used for the examination of the determinants for in-hospital mortality in the ACS population. Once the parameters proved a $p < 0{,}20$ significance level by univariate logistic regression, a multiple logistic regression was performed to examine its independent predictive role. Sensitivity, specificity, positive and negative predictive values were calculated in the standard way with 95% CI. To determine a predictive value of a parameter, the receiver-operating characteristic (ROC) was used. The correlation was confirmed by a Spearman test. The level of significance was identified as p=0.05.

4. Results

4.1. Predictive factors for mortality in cardiogenic shock

The inclusion criteria were fulfilled by 287 patients in our study. The length of hospitalization was 11.45 days on average. In-hospital mortality was as high as 26.83% in the population. Follow-up was conducted for 1 year, the one-year mortality rate was calculated as 33.45%. IABP counter pulsation was part of the therapy in 98.26% of the subjects. The length of IABP counter pulsation was 4.82 days on average, vessel complication related to the device was observed in 5.67 %.

Patients were divided into two groups based on in-hospital death. The two groups did not differ significantly regarding age, gender, CV risk status, CV conditions and previous CV endpoints or successful prehospital reanimation. Telemedicinal consultation was more frequent in the survival group (45.71% vs. 27.27%; p=0.0104). Among ischemic time intervals, the pain-to-door time was significantly longer in the hospital mortality group (26.63 ± 54.93 hours vs. 13.16 ± 25.35 hours; p<0.0001), while there was no significant difference regarding the door-to-balloon time.

To further examine the role of telemedicinal consultation, patients were divided into 2 groups based on telemedicinal consultation. Before the admission of 116 patients, ECG-based telemedicinal consultation was performed, while in the control arm data of 171 individuals without consultation were analysed. The pain-to-door time was 9.44 ± 11.21 hours in the consultation group, while it was significantly longer in the control group (23.77 ± 48.63 hours; p <0.0001). We further analysed the correlation between telemedicinal consultation and pain-to-door time intervals in the in-hospital mortality group. In this subgroup, telemedicinal consultation was performed in 21 cases, where pain-to-door time was 6.75 ± 6.77 hours long. In 56 cases of the hospital mortality subgroup without telemedicinal consultation this time duration was significantly longer (34.98 ± 62.49 hours; p=0.0065).

CS was the complication of STEMI in 74.56 % and NSTEMI in 25.44 %. The distribution of the ASC forms did not differ significantly in the two subgroups created on the basis of hospital death. Moreover, there was no difference between the two groups regarding the culprit vessel and the rate of multivessel involvement. The prevalence of PCI did not differ either, in the hospital survival group it was 73.81%, and 83.12% in the hospital mortality group. Also, there was no significant difference in the number and type of implanted coronary stents in the two groups.

In both groups the extension of the infarction was large, but the AAR did not differ significantly. During echocardiography performed at admission, LV EF was significantly higher in the survival group (36.96 ± 8.67% vs. 30.28 ± 8.37%; p <0.0001).

All three perfusion parameters were significantly higher in the survival group: LV QuBE: 160.13 ± 38.70 vs. 115.50 ± 33.31; p <0.0001, AAR QuBE: 90.11 ± 46.08 vs. 55.95 ± 30.16; p <0.0001, and 1AAR segment QuBE 8.89 ± 3.43 vs. 4.97 ± 2.28; p <0.0001.

There were no relevant differences detected in the qualitative blood values. The maximal activity of creatinine kinase (CK_{max}) was significantly lower in the surveillance group as expected (2166.47 ± 2607.36 vs. 5141.27 ± 8247.84 U/L; p=0.0038). As a mirror to kidney tissue hypoperfusion, the glomerular filtration rate (GFR) at admission was significantly lower in the hospital death group (52.71 ± 23.39 vs. 66.25 ± 22.33 ml/min; p <0.0001). There were no relevant differences detected in the iv. pharmacotherapy of CS in the two groups.

The parameters were analysed by univariate logistic regression, where longer pain-to-door time, prehospital reanimation, and elevated CK_{max} values were related to a significantly higher in-hospital mortality rate. Telemedicinal consultation, better LV EF at admission, a higher GFR value and all three perfusion parameters significantly lowered hospital mortality. From these results, the parameters characterized by a p value lower than 0.2 were selected for multiple logistic regression analysis. According to this test, telemedicinal consultation was proved to be an independent predictor of survival in the study population (OD 0.40, CI 0.21–0.76, p=0.0049) as well as the perfusion value calculated for one AAR segment (OD 0.85, CI 0.78–0.98, p=0.0178), and higher GFR at admission (OD 0.97, CI 0.96–0.99, p=0.0042).

Longer pain-to-door time interval (OD 1.010, CI 1.004–1.014, p=0.0006), prehospital reanimation (OD 1.58, CI 1.01–3.10, p=0.0411), and higher CK_{max} (OD 1.16, CI 1.04–1.30, p=0.0084) were identified as independent mortality predictors.

4.2. Examination of intracoronary physiological parameters and their correlations

In the other section of our research, 19 coronary lesions of 16 patients were examined. Patients were 59.56 years old on average. Among the comorbidities, 81.25% of the patients had hypertension, 50% diabetes mellitus, 12.5% peripheral artery disease. Lesions were interrogated in 57.89% on the left anterior descending coronary artery (LAD), 15.79% on the left circumflex coronary artery (LCx), and 26.32% on the right coronary artery (RCA). The average length of the lesions was 21.65 ± 11.69 mm, MLA was 2.13 ± 0.99 mm^2, the stenoses were 51.32 ± 11.70% on average. In three cases, PCI was also performed, where measurements were made both before and after stent implantation.

The pressure data during the resting phase as well as during maximal vasodilatation were measured proximal and distal to each stenosis, and FFR and CFR calculations were performed. FFR had on average value of 0.79 ± 0.11, and CFR value was 2.01 ± 0.61 on average. FS_i was calculated for 0.040 ± 0.028 average value.

In the three cases with PCI, FFR and FS_i values differed significantly before and after stent implantation.

FS_i had no significant correlation with CFR (r=−0.23, p=0.34). However, between FS_i and FFR a significant correlation was detected (r=−0.66, p=0.002). Interestingly, FS_i and the index obtained from the resting pressure ratio and FFR had a closer correlation (r=0.92, p <0.0001).

The prognostic power of FS_i in identifying a lesion with an FFR lower than 0.8 was examined by ROC analysis. A higher value than 0.022 of FS_i shows a pathological FFR with an 0.856 area under the curve (AUC), 95% CI 0.620 to 0.972. Positive predictive value, negative predictive value, accuracy, sensitivity, and specificity were calculated: 0.90, 0.889, 0.895, 90%, 88.89%, respectively.

5. Discussion

5.1. Predictive factors of mortality in cardiogenic shock

Early diagnosis is a critical step in the therapy of ACS in order to reduce the risk of complications. Previous studies have proved that prehospital care supported by telemedicinal tools reduces hospital mortality in STEMI. This phenomenon is related to the ischemic time, as its reduction is proportional with the improvement of LV perfusion achieved after PCI. In our study, the same results have been proved in patients suffering ACS complicated with CS; moreover, telemedicinal consultation was an independent predictor in the reduction of hospital mortality. These positive results originated from the optimization of patient transport and the preparation of the required special care by hospital staff, which together reduce ischemic time and consequently support the improvement of LV myocardial perfusion. The added value of telemedicine is crucial, as the best possible individualized therapy can be started early on in the prehospital phase on the basis of the telemedicinal consultation.

Recent guidelines emphasise early PCI strategy in ACS. The extent to which the left ventricular area is affected by the infarction in ACS is a determinant of the outcome of the disease; however, in our study population, this correlation failed to be proved. Presumably, an AAR greater than the cut-off value acts as limitation factor in this population. At the same time, as CS is related to the extension of perfusion deficiency, coronary revascularization as a definitive therapy improves perfusion. In line with this, LV perfusion values showed a close correlation with in-hospital mortality rates. All the QuBE scores are linked to the endpoint in CS. Furthermore, the perfusion value calculated for one myocardial segment in the AAR is proved to be an independent predictor of mortality by multivariate log rank analysis.

5.2. Importance and interconnections of intracoronary physiological parameters

In our research, a new index, FS_i was defined, which reflects on the different blood flow forms in IHD and its value is calculated from the pressure data of FFR measurement, and anatomic and calculated flow data obtained from 3D coronary reconstruction. Turbulent flow basically affects WSS, and consequently the progression of atherosclerotic plaques. Moreover, the dynamic changes of WSS enhance the vulnerability of the plaques in the coronary tree, so parameters representing turbulent flow draw attention to the fact that a lesion can potentially be a cause of ACS. FS_i is therefore not only informative in the determination of the actual functionality of a lesion, but it may also be identified as a potential ACS source.

In our research, significant correlation was proved between FS_i and the FFR, which, according to previous trials, has a prognostic value for IHD endpoints. This finding is in line with previous observations, as the pressure gradient examined under maximal hyperaemia is related to the pathologic flow separation. On the other hand, FFR does not describe the effect of pathologic flow during the resting state, even though low and oscillating WSS also presents during the resting phase in the area of flow separation, and according to its longer duration, this effect is much more prominent in the progression of atherosclerosis. Consequently, the incorporation of resting pressure data into the calculation makes FS_i a potentially better prognostic marker of indicating a CV endpoint as opposed to FFR calculated based on hyperaemic pressure data only.

6. Summary

The mortality rate of cardiogenic shock is especially high in acute forms of IHD. To reduce this rate, the exploration of prognostic factors is indicated, which may modify recent guidelines and positively influence the outcome of the disease. One of the main goals of the present research was to examine different prehospital and coronary physiological parameters in ACS complicated with CS. Indeed, we demonstrated, that prehospital telemedicine reduces in-hospital mortality in this patient population. It has also been confirmed, that myocardial perfusion calculated from the evaluation of coronary angiography images indicating the efficiency of revascularisation, closely correlates with in-hospital mortality. Moreover, the perfusion value projected to one segment of the left ventricular area at ischemic risk is an independent predictor of mortality in this population.

Functional examination of the coronary artery lesions is crucial to select optimal therapy, including decisions on revascularisation and the verification of the success of the therapy during follow-up. The other aim of the research was to describe an index wich identifies the severity of a lesion in relation to the entire coronary circulation, and incorporates the complex attributes of the coronary blood flow, as well. The method we utilized does so by relying on anatomical parameters from 3D coronary reconstruction and pressure data obtained from FFR measurement. The examination of the FS_i, stipulated on pressure-flow relationship, was performed. According to the results, FS_i correlates excellently with FFR, which is proven to have prognostic value in IHD and provides data on physiological characteristic of the coronary circulation. FS_i can therefore be as an important parameter in identifying the functional role of coronary lesions and estimating their progression.

In the research, the following key observations were made:

1. In the treatment of CS complicated ACS patients, prehospital telemedicinal ECG evaluation with consultation is an independent predictor of survival in this patient population.

2. The perfusion value of the area at ischemic risk projected to one left ventricular segment determined by the evaluation of coronary angiograhy images is an independent predictor of in-hospital mortality in ACS complicated with CS.

3. FS_i correlates with FFR in a model where the FS_i was determined to describe flow separation and was calculated from coronary physiological parameters during resting and hyperemic invasive examination conditions and from anatomical data obtained from 3D coronary reconstruction. Due to the inclusion of the resting flow rates in the calculation, FS_i appears to be a potentially better prognostic marker of lesion progression, and may better predict cardiovascular endpoints as well.

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8. Appendix

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List of publications related to the dissertation

1. **Szabó, G. T.**, Ágoston, A., Csató, G., Rácz, I., Bárány, T., Uzonyi, G., Szokol, M., Sármán, B., Jebelovszki, É., Édes, I. F., Czuriga, D., Kolozsvári, R., Csanádi, Z., Édes, I., Kőszegi, Z.: Predictors of Hospital Mortality in Patients with Acute Coronary Syndrome Complicated by Cardiogenic Shock.
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3. **Szabó, G. T.**: Hallgatózási alapismeretek.
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