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Multimodality perspective in cardiology: from non-invasive diagnostics to invasive therapy

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1 INTRODUCTION AND LITERATURE REVIEW

1.1 Ischemic heart disease

Ischemic heart disease (IHD) and acute coronary syndrome (ACS), latter including unstable angina pectoris, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), is still one of the leading causes of death in Europe and North America. Year 2017 data reveals that IHD affected 126 million people worldwide, which accounts for 1.72% of the world's population. In Europe, the prevalence of IHD is 3,547 per 100,000 people; and while its incidence is decreasing in Europe, it is shown to increase in Hungary. The prevalence of STEMI is stagnating, whereas that of NSTEMI is steadily increasing.

In stable angina pectoris syndrome, which is mostly caused by coronary stenosis, the balance between oxygen demand and supply to the heart becomes gradually impaired, but this process is yet reversible. In such cases, chest symptoms first appear on exertion as the stenotic segment cannot dilate sufficiently to meet the increasing oxygen demand of the myocardium. In ACS, however, there is a sudden and often irreversible disruption in myocardial oxygen supply. The most important unmodifiable risk factors for IHD include gender, age, and genetics, while the factors that can be changed or treated are obesity, smoking, unhealthy diet, sedentary lifestyle, hypertension, diabetes, hyperlipidemia, and kidney disease.

The primary condition that may lead to ischemic heart disease and eventually ACS is atherosclerosis, which starts in childhood and lasts a lifetime. Atherosclerosis is a slow inflammatory process in the subintimal space, which can be accelerated by the aforementioned risk factors. Monoclonal cells, as members of the innate immunity, play an important role in this process; their signaling molecules, located on the cell surface, help to prevent further inflammatory cells from entering the vascular wall. Furthermore, the cells themselves produce additional enzymes that promote plaque instability (cytokines, metalloproteases). A number of vasoactive substances such as histamine, leukotrienes, and T helper cells also play an important role in the atherosclerotic process. Although the process has a generalized effect on the whole vascular system, in coronary arteries it is mostly focal abnormalities that can be seen. The most affected parts of the coronary arteries are the proximal segments and the coronary bifurcations. As a hemodynamic factor impacting fibro-atheroma development, endothelial shear force plays an important role in the above phenomenon. Endothelial shear force also affects endothelial differentiation. Plaque growth and progression can occur in several ways. In the case of positive remodeling, plaques start to grow outwards, resulting in compensatory dilation of the affected vessel wall segment. In the beginning, this has no lumen narrowing effect until its volume reaches at least 40%. In the next stage, however, plaques start protruding into the lumen, which may create a hemodynamic obstruction over time. Histopathological studies suggest that positive remodeling is associated with an increase in the number of macrophages and, concomitantly, necrotic nuclei. In negative remodeling, by contrast, vascular diameter decreases, causing coronary stenosis. This type of lesion is particularly common in diabetes. Several studies have confirmed that in plaques with similar geometrical properties, the fibrous cap over positively remodeled plaques had a higher shear stress, which predisposes them to plaque rupture. Autopsy findings show that lipid-rich atheroma, which usually has a necrotic core and a thin fibrous cap, are also more prone to plaque rupture, which can lead to myocardial infarction.

In STEMI, the cause of thrombus formation is usually plaque rupture, erosion, or calcified nodules, whereas in NSTEMI the leading cause of partial or complete vascular occlusion is plaque erosion. The primary cause of plaque rupture is the thinning of the fibrous cap on the plaque due to disruption in collagen metabolism; this is followed by blood getting into the lipid-rich core, which leads to clot formation. Plaque erosion starts with endothelial cell apoptosis due to oxidative stress, which is followed by thinning of the fibrous cap and its complete disappearance in some places. For the morphological assessment of plaques coronary computed tomography (CCT) imaging can be a useful tool to detect the so-called napkin-ring sign and spotty calcifications that have a strong prognostic significance in ACS.

1.1.1 Diagnostic tests for ischemic heart disease

Non-invasive techniques

- Echocardiography: easily accessible, non-invasive, with no radiation exposure. This imaging technique can provide information on systolic left and right ventricular function, left ventricular segmental wall motion, possible valve abnormalities, and cardiac chamber dimensions.
- Stress electrocardiogram: easily available, cost-effective, with no radiation exposure, but low sensitivity. Information can be obtained on the patient's exercise capacity, blood

pressure dynamics, possible arrhythmias, and the development of ECG signs suggestive of IHD.

- Coronary computed tomography angiography (CCTA): has a wide range of indications, with coronary artery disease being the most common. CCTA scan is an X-ray test, which relies on the differences in the tissues' absorption of X-rays. Native CCTA can assess at low radiation doses the degree of coronary calcification, which can be quantified using the Agatston score for cardiovascular (CV) risk assessment. By adding a contrast agent and preparing the patient appropriately (low pulse), a suitable and ECG-guided CT can diagnose the extent of coronary artery disease with good sensitivity. The negative predictive value of coronary CT is nearly 100%. In patients with acute chest complaints, when ACS is not established, a "triple rule out" examination can be performed for the three signs of chest catastrophe in a single CT scan: ACS, pulmonary embolism, and aortic dissection. CCTA can also be used for high-resolution morphological and functional imaging, a major aid in various structural interventions and electrophysiological procedures, which are becoming increasingly widespread.

- Stress myocardial perfusion scintigraphy (SPECT): a test using radiation to provide information on the perfusion capacity of the myocardium after the injection of radioactive isotope labeled tracers.

- Dobutamine stress echocardiography (DSE): two-dimensional (2D) echocardiography with pharmacological stress. During the examination, myocardial contractility on dobutamine administration is monitored continuously with ECG. If dobutamine causes left ventricular segmental hypokinesia, it can be assumed that the coronary artery supplying the given area is stenotic.

- Dobutamine stress magnetic resonance imaging: It works in a way similar to the DSE test. The main diagnostic advantage of cardiac magnetic resonance imaging (CMRI) is for patients in whom echocardiography cannot provide an adequate image.

- Viability testing by CMRI: in post-infarction patients, it can provide information on the viability of the coronary artery supply area. This technique can help, for example, in the case of a chronic total occlusion, to decide whether the vessel should be opened. It requires the use of a contrast agent (gadolinium). In healthy myocardium with preserved vascularization, the contrast agent is only visible in the myocardium for a few minutes, after which it washes out. In damaged myocardium, however, complete washout (disappearance) of the contrast agent can take up to 20-30 minutes. Thus, images taken 10-15 minutes after contrast injection (delayed enhancement images) can show the extent of myocardial damage/scarring.

Invasive techniques

- Coronary angiography: the gold standard test for the examination of coronary arteries. Its advantage is that it serves both diagnostic and therapeutic purposes, if necessary. Its disadvantage, on the other hand, is that it is invasive and involves radiation exposure. The examination is performed through an artery (radial or femoral), through which the coronary ostia are cannulated. After contrast medium administration, the coronaries are imaged with the help of an X-ray tube. In the case of ACS, coronary angiography and percutaneous coronary intervention (PCI), if necessary, should be performed as soon as possible.
- Fractional Flow Reserve (FFR): a physiological index that can be determined during coronary angiography. A special wire is used to measure the pressure in front of and behind the stenosis at maximum vasodilation. FFR is the ratio of mean coronary pressures measured distal and proximal of the stenosis; and a value below 0.8 is indicative of significant coronary stenosis. The FFR-guided revascularization strategy is clearly more reliable than visual assessment.
- Intravascular ultrasound (IVUS): the gold standard procedure for plaque analysis. During coronary angiography, an IVUS catheter is introduced into the coronary lumen, which makes it possible to separate vessel wall layers, and provide precise information about the morphology of the plaques.
- Optical coherence tomography (OCT): during OCT, an optical probe provides information about the inner surface of the vessel with the help of the interference generated by light scattering.

In ACS, the diagnostic procedure of choice is still coronary angiography followed by PCI, as needed and feasible, more precisely stenting. The effects of stent placement in native coronary arteries have been widely studied. Stenting leads to changes in the geometry of coronary vessels. In our previous study, we found that parameters obtained through 3D reconstruction of 2D invasive angiography images can provide valuable information. It has been demonstrated, among others, that the percent of coronary stenosis area and plaque volume correlate well with FFR.

The functional assessment of stenoses found TIMI (Thrombolysis in Myocardial Infarction) flow and TIMI frame count (TFC) to be useful tools. TFC measurement is based on the number of frames required for the injected contrast agent to appear at the origin of the coronary artery, and the number of frames it takes to reach the end of the coronary artery. There are three TIMI flow grades. TIMI 0 means no antegrade flow in the coronary artery. In TIMI 1, the contrast material enters the vessel, but does not reach the distal segment. In TIMI 2, the contrast agent flows through the affected coronary artery at a reduced speed, while in TIMI 3 coronary flow is normal. The occurrence of TIMI 0-2 in ACS is estimated to be around 15-26%. French et al. found that the TFC value measured three weeks after PCI is an independent predictor of five-year survival. In addition, they noted that with SPECT, perfusion defect size correlated well with increased TFC value.

A number of studies investigated the role of coronary thrombus and plaque material embolization, with both device-oriented and pharmacological prevention methods. Device-oriented methods included thrombus aspiration with the help of a special catheter technique, while pharmacological treatment refers to the use of intravenous platelet aggregation inhibitors. Farooq et al. hypothesized that certain aspiration methods could prevent macroembolization (when plaque material embolism occurs on epicardial artery level), whereas others might reduce the rate of microembolization on capillary level, thus reducing the development of potential slow- or no-reflow. Tanaka et al. consider coronary microembolization to be the definite cause of slow coronary flow or no-reflow. In the case of no-reflow, the coronary flow in the affected segment is insufficient, but no clear mechanical obstruction can be identified. Most previous studies were conducted on models, using 3D reconstructions, and in patients with stable coronary artery disease, and not with ACS.

1.2 Aortic stenosis

Aortic stenosis (AC) is the most common primary valve disease, and its prevalence increases with age, affecting primarily the elderly. The normal aortic valve consists of three leaflets, including the right coronary cusp (RC), left coronary cusp (LC), and non-coronary cusp (NC). In cases of congenital abnormality, however, which affects approximately 2% of the population, the aortic valve only has two leaflets. In such cases, it is referred to as a bicuspid aortic valve.

In the developing world, AS can also be caused by rheumatic fever, but generally the most common cause is a slow, progressive calcification process. In the initial stages, the valve thickens, and calcification starts. Over the years, calcification advances to a point when it impedes the movement of the valve, causing flow obstruction. The initial stage of AS is prolonged and practically symptom-free. During this phase, the heart adapts to the deterioration of left ventricular outflow tract obstruction by developing myocardial hypertrophy. In this compensatory process, there is a transient increase in the left ventricular systolic function; however, concurrently, the diastolic function deteriorates. Nevertheless, this compensatory mechanism can only sustain an adequate stroke volume for a limited period. Over time, the cardiac muscle starts to wear out, the systolic function gradually decreases, and symptoms characteristic of heart failure begin to manifest: shortness of breath, reduced exercise tolerance, chest pain, dizziness, fainting, arrhythmias, and edema. Following the onset of symptoms, the patient's condition usually deteriorates rapidly.

To determine the severity of AS, the diagnostic method of choice (gold standard) remains echocardiography. The severity of AS can be estimated on the basis of three parameters: the mean (MG) and peak pressure gradients (PG) across the valve, the maximum flow velocity across the aortic valve (V_{max}), and the aortic valve area (AVA). Generally, AS is considered severe when AVA ≤ 1 cm^2, MG > 40 mmHg, and $V_{max} > 4$m/s.

Based on echocardiography parameters, AS can be categorized into four groups: high-gradient AS, low-flow/low-gradient AS with preserved systolic left ventricular function, low-flow/low-gradient AS with reduced systolic left ventricular function, and normal-flow/low-gradient AS with preserved systolic left ventricular function.

In nearly one-third of patients, in whom AVA$\leq$1cm^2, V_{max} and pressure gradients do not necessarily correlate with the AVA.

In these cases, determining the right time for valve replacement often poses a challenge. This, in turn, raises the need for another diagnostic method to be able to precisely assess the degree of severity.

The latest CCTA techniques, which focus on the stenotic/calcified aortic valve, can provide assistance in diagnosis when echocardiography results are inconclusive.

As shown by both *in vitro* and *in vivo* studies, the aortic flow in a healthy aortic valve is helical with end-systolic retrograde flow in areas where the kinetic energy of the blood is high.

This phenomenon can usually be observed at the greater curvature of the ascending aorta. The helical character is crucial for optimizing the flow to prevent flow instabilities in the aorta. In the case of severe aortic stenosis (SAS), the blood flow velocity increases, resulting in an eccentric flow across the aortic valve and an unphysiological helical flow pattern. As a result of these flow pattern changes, ascending aorta dilation and dissection may occur, whereas on a cellular level, platelet activation and thrombus formation can result.

In the past, surgical aortic valve replacement (SAVR) involving open chest approach used to be the only solution for treating SAS. Recently, however, transcatheter aortic valve replacement (TAVR) was introduced as an alternative method for special cases and patient groups. TAVR is primarily performed on patients with a high surgical risk. TAVR is favored when the patient is of advanced age with comorbidities that increase surgical risk, such as renal failure, heart failure, diabetes, and severe lung disease. Besides the aforementioned factors, TAVR should also be preferred in cases of history of cardiac surgery, history of chest radiation, porcelain aorta, or severe chest deformity. Prior to the intervention, it is mandatory to perform CCTA to assess anatomy and calculate the precise size of the valve. In addition, planning the access route requires aorta and lower extremity CTA. The femoral artery is most commonly chosen for access, but in cases of significant calcification and stenosis, alternatives like transaortic, transapical, or carotid artery access may also be considered. The introduction of CCTA examinations has helped prevent various complications, of which peripheral vascular injuries were the most common.

2 OBJECTIVES

In the first part of our examinations, we created 3D reconstructions from 2D coronary angiograms, which were analyzed for STEMI and NSTEMI.

Our hypothesis was that the 3D parameters of coronary stenosis and plaques/lesions, especially the smallest luminal parameters like area and diameter, could predict flow changes occurring in ACS.

We also hypothesized that there might be post- PCI flow differences between the two main forms of ACS (STEMI and NSTEMI) due to differences in plaque morphology and composition between the two groups.

Last, but not least, we anticipated a correlation between the extent of post-PCI changes and 3D parameters.

Furthermore, we investigated which subgroup of patients might require additional therapy for improving post-PCI coronary flow, either through a device or a pharmacological intervention, such as the use of glycoprotein (GP) IIb/IIIa receptor inhibitors.

In the second part of our examinations, our hypothesis was that hemodynamic changes in patients with SAS could have an impact on the contrast density measured in CCTA in perivalvular regions, meaning that density values would differ between patients with SAS and those with a normal aortic valve (NAB).

Secondly, we hypothesized that in SAS the density values measured during CCTA might correlate with parameters measured by echocardiography.

3 PATIENT INCLUSION AND METHODS

3.1 Assessment of culprit vessel flow and the 3D parameters of the plaque in acute coronary syndrome

In the first part of our examinations, patients treated at the Cardiology and Heart Surgery Clinic at the Clinical Center, University of Debrecen, were included, who had experienced acute myocardial infarction, altogether 71 STEMI and 73 NSTEMI patients. All patients had undergone coronary angiography and PCI including stent implantation as part of acute event management. We also considered the patients' demographic data (age, gender), relevant cardiovascular risk factors (smoking, obesity, hypertension, diabetes, history of acute myocardial infarction, PCI), and the use of sodium heparin (Na-heparin) in the framework of the pharmacological therapy received during pre-hospital care. The data were extracted from the clinical information system (MedSolution, T-Systems, Frankfurt, Germany).

All coronary angiography examinations were performed in the hemodynamic laboratory of our Clinic using the GE Innova System (GE Healthcare, Chicago, IL, USA), with an acquisition speed set at 15 frames per second. Omnipaque 350 mg/mL (GE Healthcare, USA) or Visipaque 300 mg/mL (GE Healthcare, USA) were used as contrast agents at a rate of 3 mL/sec and a volume of 6 mL. Patients with TIMI 0-1 flow during initial assessment were excluded from the study.

As a first step, TFC was employed for the objective measurement of coronary flow velocity. TFC measurements were performed three times before and after coronary intervention, and the average values were calculated.

In the second step, from the coronary angiography images two angiograms of the culprit vessel segment were selected after making sure there was a minimum angular separation of 25 degrees. On both images the most proximal and distal disease-free segments of the culprit vessel were identified. Subsequently, 2D and 3D coronary and plaque reconstructions were performed on the segment between these two points using the QAngioXA 3D (QAngio®XA 3D Research 1.0 edition, Medis Specials bv, Leiden, Netherlands) program.

In the third step, the correlation between TFC and 3D parameters was investigated within the STEMI and NSTEMI subgroups, as well as between the two groups.

3.2 Determination of aortic stenosis severity by CCTA

Every enrolled patient first presented at our Clinic's outpatient department, where after demographic data collection, medical history recording, and a physical examination, echocardiography was performed.

Patients with AVA ≤1 cm^2, that is patients with SAS, were assigned into the first group. Based on comorbidities and other parameters TAVR was indicated; therefore, CCTAs were conducted in line with the protocol. The first group is hereafter referred to as SAS.

For the second group, the inclusion and exclusion criteria were the same as in the first group, except that AVA was >1 cm^2, and the transvalvular peak velocity was ≤2.5 m/s. These patients had previously undergone CCTA for coronary evaluation based on the indication of chronic coronary disease. The second group is hereafter referred to as NAV (normal aortic valve).

Exclusion criteria were defined as not consenting for CCTA and having a bicuspid aortic valve defined by echocardiography, as well as aged < 18. Low-flow, low-gradient AS cases were also excluded from the investigation.

Based on the above, 40 and 15 patients were included in the SAS and NAV groups, respectively. The time interval between echocardiography and CCTA was less than 6 months in all cases.

The severity of aortic stenosis was evaluated by standard echocardiography measurements. To define AVA the following continuity equation was used:

$$AVA = \frac{LVOT\ VTI \cdot \pi \cdot (LVOTd/2)^2}{AoVVTI}$$

where LVOT VTI represents the left ventricular outflow tract velocity time integral, LVOTd is the left ventricular outflow tract diameter, and AoVVTI is the aortic valve velocity time integral. The MG and PG values measured across the valve were obtained using continuous wave Doppler. The grade of aortic regurgitation was defined by visual evaluation (0–4), while left ventricular ejection fraction (LVEF) was defined by the Simpson biplane method.

Every CCTA was performed with a GE Lightspeed 64-detector VCT (GE Healthcare, Boston, MA, USA) with the helical mode in the retrospective ECG-triggered mode; a tube voltage of 100 kV, with the current adjusted automatically, and a slice thickness of 0.625 mm. Omnipaque 350 mg/ml (GE Healthcare, Boston, MA, USA) contrast agent was administered. The SAS patient group received 40 mL of contrast agent at a rate of 2.5 mL/s, while the members of the other group received 50 mL of contrast agent at a rate of 5 mL/s. After contrast agent administration, 50 mL of normal saline was injected at a rate of 5 mL/s in both groups via an 18G line inserted into the right middle antecubital vein. Image reconstruction was conducted at a 20% RR interval as the highest flow through the most widely opened valve is approximately 200 msec after the start of the QRS. Contrast densities were measured by both an expert radiologist and an imaging cardiologist in a blinded fashion with an AW Server workstation (GE Healthcare, Boston, MA, USA) in Hounsfield units (HU) in twelve different regions in 3D reconstruction mode:

a. 4–5 mm above the opening of the aortic valve (AAV)

b. at the junction of the leaflets and the fibrotic annulus (left, AL; right, AR; and non-coronary, AN)

c. the mid-level of the sinus of Valsalva at the most lateral (Valsalva lateral left, VLL; Valsalva lateral right, VLR; and Valsalva lateral noncoronary, VLN) and at the mid-point (Valsalva center left, VCL; Valsalva center right, VCR; and Valsalva center non-coronary, VCN)

d. in the midline of the sinotubular junction (STJ)

e. and 4 cm from the sinotubular junction (4STJ)

Each region of interest was 3-5 mm². Patients with severe calcification limiting the evaluation were excluded.

Four pathways were defined for the evaluation of results:

1. Evaluation of density values measured in the 12 regions between groups and independently of the group

2. Density differences between the two groups for each region

3. Possible correlation between the echocardiography and CCTA density parameters in SAS patients.

4. Possible effects of demographic data on CCTA densities

4 RESULTS

4.1 Assessment of culprit vessel flow and the 3D parameters of the plaque in acute coronary syndrome

Significantly more STEMI patients received pre-hospital sodium-heparin (79 *vs*. 22%, $p<0.001$), whereas diabetes (21 *vs*. 45%, $p=0.002$), dyslipidemia (18 *vs*. 56%, $p<0.001$), and previous myocardial infarction (11 *vs*. 37%, $p<0.001$) were significantly more common in NSTEMI patients.

In case of the intergroup comparison of pre- and post-PCI TFC, we found markedly, but non-significantly higher pre-PCI TFC in STEMI patients (32.42±14.49 *vs*. 28.34±10.57; $p=0.056$). We found no significant differences is post-PCI TFC.

Evaluating the intragroup results, we found that as coronary flow improved significantly after the intervention, post-PCI TFC decreased significantly in STEMI (32.42 *vs*. 24.37; $p<0.001$), whereas in the NSTEMI group post-PCI TFC decreased in a non-significant manner (28.34 *vs*. 26.89; $p=0.324$).

When looking at 3D parameters, there were no significant differences between the STEMI and NSTEMI groups.

In the second part of our investigation, the patients were divided into two groups based on changes in post-PCI TFC. Patients with an increase in TFC with at least 3 frames (group

$\Delta \geq 3$), which indicates a significant decrease in coronary flow, were included in the first group. The second group included patients with an increase in TFC with 1 or two frames, no change in TFC, or a decrease in TFC (group $\Delta < 3$), which is indicative of a mild decrease, no change, or increase in coronary flow.

We observed significantly more NSTEMI patients in the $\Delta \geq 3$ group (12 *vs*. 59 for STEMI and 26 *vs*. 47 for NSTEMI p=0.010). Also, patients receiving sodium-heparin during pre-hospital treatment belonged significantly more often to the $\Delta < 3$ group (13 *vs*. 59; p=0.023).

Afterwards, we performed intragroup investigations in the STEMI and NSTEMI groups depending on $\Delta \geq 3$ or $\Delta < 3$. In the STEMI group, we found no significant differences either in demographics or 3D parameters.

During the NSTEMI intragroup investigations we found no differences in demographics between the $\Delta \geq 3$ and $\Delta < 3$ groups. Regarding 3D parameters, however, we found that MLD (1.07 ± 0.32 *vs*. 0.87 ± 0.24; p = 0.007) and MLA (1.49 ± 0.68 *vs*. 1.04 ± 0.52; p = 0.002) were significantly greater in the $\Delta \geq 3$ group. Percent diameter obstruction at MLD (50.57 ± 14.11 *vs*. 58.80 ± 10.85; p = 0.007), percent area obstruction at MLD (55.52 ± 20.31 *vs*. 69.42 ± 13.68; p = 0.001) and area obstruction at MLA (60.66 ± 16.55 *vs*. 71.29 ± 12.61; p = 0.003) were significantly greater in the $\Delta < 3$ group.

Furthermore, we investigated mortality and the use of GP IIb/IIIa receptor inhibitor. Only one patient died before discharge in the NSTEMI group, and there were 3 cases of in-hospital mortality in the STEMI group. Long term follow-up (6 years) results showed no significant differences in mortality between the STEMI and NSTEMI groups (p = 0.789). As regards GP IIb/IIIa inhibitor use, there was no significant difference between those who received GP IIb/IIIa inhibitor treatment and those who did not; however, there was a trend of better survival in the GP IIb/IIIa inhibitor group.

4.2 CCTA evaluation of aortic stenosis severity

First, we compared patients' demographics, which revealed that SAS patients were significantly older.

Only mild/moderate aortic regurgitation was present, but still significantly higher values were seen in the SAS group (0.875 ± 1.018 *vs*, 0.077 ± 0.277, p = 0.006).

Second, we performed measurements on CCTA images in all 12 regions in both groups. Regardless of group, significantly higher density values were found in central parts (AAV, VCR, VCL, VCN, 4STJ) compared to lateral regions in every patient. We also found significantly higher densities in all the regions in the NAV group compared to the SAS group.

All CCTA measurements were performed by two different specialists (an imaging cardiologist and an expert radiologist). Two methods were employed to confirm that at least acceptable and, in certain cases, good interobserver reliability could be observed in almost all regions.

Intraclass correlation coefficient (ICC) calculation showed significant agreement between the investigators in all regions.

Bland–Altman plot results proved that apart from measurements at the AN, VLN and VLR regions, good agreement was found between the two investigators. It can also be noted, that apart from the AN and the 4STJ regions, one of the investigators always measured higher values.

Third, we investigated the correlation between echocardiography parameters (MG, PG, AVA, $V_{max,}$ LVEF, aortic regurgitation) and densities in CCTA.

We found a significant correlation between the AVA and the densities in eight regions, at the AR (p=0.020), AL (p=0.044), VLR (p=0.006), VLN (p=0.060), VCR (p=0.006), VCN (p<0.001), STJ (p=0.011) and 4SJT (p= 0.004). Only AAV, VLL, and VCL did not show any correlation with AVA.

Density in the VLR region showed significant correlation with all echocardiography parameters used for the evaluation of AS (MG: p=0.004; PG: p= 0.024; V_{max}: p=0.008; AVA: p=0.009).

Density in the AN region showed marked yet non-significant (p=0.06) correlation with the AVA, but a significant correlation with the rest of the echocardiography parameters used for grading aortic stenosis (MG: p =0.027; PG: p = 0.037; V_{max}: p=0.031).

LVEF and aortic regurgitation showed no correlation with densities.

With regard to right ventricular outflow tract densities, no difference was found between the two groups: 151.93 ± 58.33 *vs*.144.67 ± 65.20, p = 0.607. In the case of left ventricular outflow tract densities, however, significantly higher values were detected in the SAS group: 374.36 ± 118.99 *vs*.269.48 ± 61, $p = 0.001$.

In all regions, sensitivity, specificity, Youden index, and AUC values were measured at the cut-off values. For all *p* values at cut-off densities, the level of prediction was significant in all regions.

5 DISCUSSION

5.1 Assessment of culprit vessel flow and the 3D parameters of the plaque in acute coronary syndrome

NSTEMI patients suffered from significantly more comorbidities (hypertension, diabetes, previous myocardial infarction), while sodium-heparin use in ambulance was more significant in the STEMI group, which is no surprise as it is part of the STEMI management protocol.

In case of intergroup comparison, we found marked yet not significantly higher pre-PCI TFC in STEMI patients, which was probably due to higher dispensed thrombus burden.

Our intragroup comparison showed that the flow improved significantly after PCI in the STEMI group, which means that TFCs decreased significantly. The decrease in TFCs was not significant in the NSTEMI group, which may have resulted from plaque caused microembolization impairing capillary circulation to a greater extent.

Umman et al. showed a strong correlation between TFC and FFR, proving that post-PCI TFC decrease and FFR increase support each other towards successful revascularization. Hayıroğlu et al. investigated whether post-intervention TFC change could affect the outcome in cardiogenic shock patients with STEMI and found TFC $\Delta \geq 2$ (i.e., flow decreases significantly) to be an independent predictor of mortality. Considering the above studies, we can conclude that functional parameters, such as FFR and TFC, correlate well with several 3D parameters and mortality. In our previous paper, we proved that in stable coronary disease patients, 3D parameters like area obstruction and plaque volume correlate well with FFR.

The examination of 3D parameters found no significant differences between the two groups, which refers to fairly similar plaque morphology characteristics, giving partial answers to our query with regards to plaque characteristics in different forms of ACS in STEMI and NSTEMI.

When we created the TFC Δ≥3 and TFCΔ<3 groups, we found that significantly more NSTEMI patients got included into the Δ≥3 group, while patients receiving sodium-heparin belonged significantly more often to the Δ<3 group.

When evaluating the 3D parameters, we found that MLD, MLA, and reference diameter at MLD were significantly greater in the Δ≥3 group. It might sound paradox that greater lumen, hence smaller plaque volume causes decreased coronary flow after intervention, but it is probably due to plaques with multiple, hemodynamically non-significant lesions providing more debris compared to plaques with one more severe, but “lonely” lesion.

Afterwards, we performed intragroup investigations in the STEMI and NSTEMI groups considering Δ≥3 or Δ<3 grouping. We found no significant differences between the two subgroups in STEMI patients. In NSTEMI patients, the differences were similar to the Δ≥3 group regardless of ACS form, as the majority of the Δ≥3 group consisted of NSTEMI patients. As regards odd ratio, greater MLD and MLA proved higher risk for significantly decreasing post-intervention coronary flow (Δ≥3).

Only one patient died before discharge in the NSTEMI group, and there were 3 cases of in-hospital mortality in the STEMI group. Low in-hospital mortality figures can be explained by the fact that no patient arrived in cardiogenic shock, and TIMI 0 and 1 patients were excluded. Our long-term follow-up results were in line with the literature.

As regards GP IIb/IIIa inhibitor use, there was no significant difference between those who received GP IIb/IIIa inhibitor treatment and those who did not; however, there was a trend of better survival in patients receiving GP IIb/IIIa inhibitor. The same trend could be seen in the STEMI group and having no death at 6^{th} year in patients receiving IIb/IIIa receptor inhibitor indicates safe use.

All the above findings raise the question of what can be done in a subset of patients with these parameters to improve post-PCI coronary flow. A potential solution is the administration of GP IIb/IIIa receptor inhibitor. In the last two decades, however, the role of GP IIb/IIIa receptor inhibitors in ACS has changed markedly.

Regarding NSTEMI, Tricoci et al. found that the administration of GP IIb/IIIa receptor inhibitor provided a significant but modest ischemic benefit. Sciahbasi et al. also declared that early administration of GP IIb/IIIa receptor inhibitors in NSTEMI was associated with significant reduction in ischemic events.

With regards to the relationship between STEMI and GP IIb/IIIa receptor inhibitors, de Luca et al. found in one of their studies in the 30-day mortality that the agent has strong recommendation in high-risk patients. In another study they also proved that early administration of GP IIb/IIIa receptor inhibitors in STEMI and PCI was associated with significant benefits in vascular endpoints and ST-segment resolution.

5.2 CCTA evaluation of aortic stenosis severity

The comparison of patients' demographics revealed that SAS patients were significantly older. This result is no surprise; as mentioned in the introduction, the most common cause of aortic stenosis is calcification, which is a long process, so this disease mainly affects the elderly.

In our investigations, we found that regardless of a normal or diseased valve, the densities are always higher in the central areas than in the lateral regions. Densities in all perivalvular regions were higher in normal aortic valve patients.

In SAS patients a significant difference was found between the aortic valve opening area and the densities in almost all regions. The densities at the mid-level lateral of the right sinus of Valsalva showed good correlation with echocardiography values used for grading aortic valve stenosis.

Our hypothesis was that the increased velocity of the blood flowing across the severely stenotic aortic valve should influence the contrast densities in the perivalvular region. We also assumed that the observed density changes may correlate with the echocardiography parameters used for grading the severity of aortic valve stenosis.

The literature was thoroughly investigated, and findings show that several fluid dynamic models have successfully investigated the flow and pressure changes in the stenotic aortic valve. Based on *in vivo and vitro* measurements, in the case of a normal aortic valve, usually no energy transformation takes place when the blood flows from the left ventricle to the ascending aorta. In the case of aortic stenosis, however, AVA decreases, the jet flow intensifies, and the kinetic energy of the flow increases. As the blood reaches the lateral parts of the sinus of Valsalva and the arc of the ascending aorta, the flow decelerates, and partial pressure (static) energy recovery takes place. Based on Traeger et al., we can define the role of the stenotic valve in pressure drop, which is termed as the valve resistance index (IVR). Calculations show that an AVA of

0.9 cm^2 can result in an IVR of 0.9; in other words, 90% of the pressure drop is due to the stenotic valve.

Taking into consideration all the above, it can be easily understood that in the peri-jet area the flow increases with every systole, and high-density regions form quickly, whereas in the remote/lateral perivalvular regions, where the flow decelerates, a slower increase in density will take place.

As the indications for CCTA were different in the two groups, we applied different protocols using different iodine delivery rates (IDR). Therefore, the question may arise as to whether the different injection parameters caused the density differences between the two groups. Lell et al. compared the enhancement from the pulmonary trunk to the branches of the aorta with different injection protocols and parameters. They changed variables including the injection speed, kV, and IDR at varying degrees. Based on their results, there were no significant enhancement differences in the pulmonary trunk. In the ascending aorta, the protocol using the highest IDR with the lowest kV (70) resulted in significantly higher densities, with an average difference of approximately 120–130 HU. In our investigation, we used the same kV of 100 with different IDRs (0.75 g/s vs. 1.5 g/s in the stenotic vs. normal valves, respectively), which resulted in approximately 130 and 150 HU differences between the two groups. From this result we assume that even by using the same injection protocol (same kV and IDR) for both groups, we would still see these differences.

Additionally, there was no density difference between the two groups in the RVOT region, probably because contrast medium dilution had already started, making the HU close to the normal blood value. In the case of the LVOT, there was a significantly higher contrast density in the SAS group, which explains the lower perivalvular density values in this group.

When evaluating the correlations between the echocardiography and the CCTA measurements, only at the mid-level lateral of the right sinus of Valsalva did we find a significant correlation between the density and all four parameters measured by the echocardiography. The explanation behind this is the fact that the greater curve of the ascending aorta is on the right, and the jet heads in this direction. Therefore, more stability can be seen in this region than on the other side of the jet.

Of the echocardiography parameters, only AVA had a significant correlation with the densities in all the regions. The most probable explanation is that the density and the distribution of calcium deposits inside the degenerated aortic valves change from patient to patient. As the orientation of the turbulent flow coming from the ventricle can exhibit a high degree of variability, the degree of valve degeneration may produce inconsistent echocardiography values, mainly in the case of the flow gradients measured across the aortic valve, as well as $V_{max.}$ On the other hand, AVA is the most stable parameter calculated from time integrals, the LVOT VTI and AOV VTI, thus shows less patient-to-patient variation. Calcium scoring would be a possible way to quantify the grade of valve calcification.

As CCTA would represent a new diagnostic method in AS, we investigated its efficacy using ROC analysis and Youden's index, which can evaluate the diagnostic value of a method in terms of sensitivity and specificity. A Youden's index above 0.5 qualifies a diagnostic method appropriate for clinical use. In our investigation, the Youden index was always above 0.6833, which suggests that CCTA as an alternative method seems promising in the diagnosis of SAS.

Of all the regions, AAV provided the best statistical result. The reason behind might be that it is in this region that the jet has the highest similarity in all patients due to geometrical stability. Based on the above, this region might be the optimal for the diagnosis of severe aortic stenosis.

Our results suggest that CCTA can be a promising complementary diagnostic method in SAS. As mentioned before, in one-third of the cases, the diagnosis of severe aortic stenosis is unclear, as the values measured with echocardiography are conflicting. In these cases, CCTA parameters, with excellent reproducibility, can help differentiate between significant and non-significant AS, especially when cardiac MRI is not available to clarify the issue. Even with these findings above, it should be mentioned that echocardiography is still the examination of choice as it is the most cost-effective, fastest, most easily accessible, very sensitive, and most specific method for the diagnosis and follow-up of aortic stenosis.

5.3 Limitations

TFC values may be affected by factors such as heart rate, the phase of the cardiac cycle at the time of contrast agent injection, and the amount of administered nitrate.

One of the major limitations of the investigation was the low sample number, which was due to the fact that most measurements were made at 20% RR interval, when the aortic valve is completely open. This reconstruction, however, requires retrospective investigation, which results in higher radiation exposure.

As the indications were different, the two patient groups were investigated using different administration protocols with different contrast agent volume and injection speed. Even though the literature shows that different protocols might not change the enhancement, to be objective, the same parameters/settings should be used when an investigation is performed.

As the cubital vein was not always available, other venous access points needed to be used, which might have an effect on densities due to smaller lumen veins or longer route to the heart.

The patients who did not have high-gradient SAS were excluded from our study.

In the future, measuring both Agatston score and the densities, or even combing the power of both, might give even better predictive value to the evaluation of AS.

5.4 New investigation results

- In acute coronary syndrome, the TFC values of the culprit vessel/segment and the 3D parameters are good predictors of revascularization outcomes.
- Considering 3D parameters, the greater the minimal lumen diameter and area (narrowest point of the occlusion), the greater the chance of post-interventional decrease in coronary flow.
- We confirmed with CCTA performed in 12 measurement regions that the density values are significantly higher in central areas.
- Also, we measured significantly lower densities in all 12 measurement regions in SAS compared to normal valve cases.
- In SAS, a significant portion of perivalvular densities measured by CCTA showed correlation with the aortic valve opening area measured by echocardiography, and one region's density value exhibited a significant correlation with all echocardiography parameters.

6 SUMMARY

In the first part of our investigation, the flow changes of the culprit segment before and after the intervention in STEMI and NSTEMI patients using 3D reconstruction were investigated. Based on the results, several characteristics of the culprit region can determinate the outcome of the revascularization: the greater the diameter and area at the narrowest point, the lesser chance there is to have improved flow after the intervention. Based on these results, in the catheterization laboratory with a specialized software, in a few minutes one can get 3D coronary parameters, and with the TFC measurements possible success of the revascularization can be predicted. In those cases, when the post-in intervention flow decrease significantly (TFC $\Delta \geq 3$), or the minimal lumen diameter and area are „less” narrow, than GP IIb/IIIa receptor inhibitor might have a positive effect on the flow.

In the second part of the research, patients with normal and significantly diseased aortic valve have been investigated with CCTA, registration the contrast densities in the Valsalva sinus and the ascending aorta. In both groups, for all 12 regions, the densities were significantly higher in the central aortic jet area. In the SAS group, in all 12 regions the densities were significantly lower, and most of the perivalvular densities showed good correlation with the aortic valve opening area by echocardiography, highlighting one region that provided significant correlation with all echocardiography parameters. In those cases, when the severity of the aortic valve stenosis is not clear, CCTA can be and adjunctive investigation, or can provide details about the aortic valve in cases when the indication of CCTA is not of valvular.

Based on our investigation, it can be concluded, that in the diagnosis of heart disease one should not necessary be satisfied with a single investigation method. With the rapid improvement of medical soft- and hardware, it became possible to apply more imaging method the secure the most accurate diagnosis.

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List of publications related to the dissertation

1. **Rácz, Á.**, Szabó, G. T., Papp, T., Csippa, B., Gyurki, D., Kracskó, B., Kőszegi, Z., Kolozsvári, R.: Potential Clinical Usefulness of Post-Valvular Contrast Densities to Determine the Severity of Aortic Valve Stenosis Using Computed Tomography.
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2. **Rácz, Á.**, Rácz, I., Szabó, G. T., Üveges, Á., Kőszegi, Z., Penczu, B., Kolozsvári, R.: The Effects of Percutaneous Coronary Intervention on the Flow in Acute Coronary Syndrome Patients-Geometry in Focus.
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List of other publications

3. Nagy, L. T., Jenei, C., Papp, T. B., Urbancsek, R., Kolozsvári, R., **Rácz, Á.**, Ráduly, A. P., Veisz, R., Csanádi, Z.: Three-dimensional transesophageal echocardiographic evaluation of pulmonary vein anatomy prior to cryoablation: validation with cardiac CT scan.
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