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Rīgas Stradiņa universitāte

Maija Radzina

BRAIN PERFUSION IN ACUTE STROKE PATIENTS WITH ATHEROSCLEROTIC CHANGES IN BRACHIOCEPHALIC BLOOD VESSELS

Summary of Doctoral Thesis
for obtaining the degree of a Doctor of Medicine
Speciality – Diagnostic Radiology

Riga, 2014

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Dr. med., Associate Professor **Ilze Strumfa**

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LIST OF ABBREVIATIONS

ASPECTS	–	Alberta Stroke Program Early CT Score
CBF	–	cerebral blood flow
CBFr	–	relative cerebral blood flow
CBV	–	cerebral blood volume
CBVr	–	relative cerebral blood volume
CDPC	–	Center of prevention and control of diseases of Latvia
CI	–	cerebral infarction or acute cerebral ischemic stroke
Core	–	latin „core" – irreversible cerebral ischemia, necrosis zone
CT	–	computed tomography
CTA	–	computed tomography angiography
CTP	–	computed tomography perfusion
DSA	–	digital subtraction angiography
ICA	–	internal carotid artery
MCA	–	middle cerebral artery
MIP	–	maximum intensity projection
MR	–	magnetic resonanse
mRS	–	modified Rankin scale
MTT	–	mean transit time
MTTr	–	relative mean transit time
NASCET	–	North American Symptomatic Carotid Endarterectomy Trial
NCT	–	non-enhanced brain CT
NIHSS	–	National Institutes of Health Stroke Score
Penumbra	–	latin „partial shadow" – potentially reversible cerebral ischemia, tissue at risk
TIA	–	transient ischemic attack
TOAST	–	*Trial of Org 10172 In Acute Stroke Treatment*
VBT	–	vertebrobasilar artery or posterior circulation territory

INTRODUCTION

Acute cerebral ischemic stroke or cerebral infarction (CI) is one of the leading causes of death, dementia and disability all over the world [AHA Heart Disease and Stroke Statistics update, 2012]. In Europe, the incidence of acute cerebral infarction (CI) is 1.1 million inhabitants per year and varies from 100 to 200 per 100,000 inhabitants [European Registers of Stroke, 2009]. In Latvia, acute ischemic stroke is a cause of death for 116 per 100,000 people [CDPC data, 2011].

Morbidity, mortality and disability rates of acute ischemic stroke remain high despite the existence of numerous significant achievements in treatment and prevention of stroke. Promotion of appropriate and timely approach to patient treatment is recommended as one of potential solutions for this problem [National Stroke Foundation guidelines, 2010].

Recent cerebral hemodynamics studies focus on the role of arterial blood flow territory in cerebral perfusion in patients with acute cerebral ischemic stroke [van Laar et al., 2008]. Latest available technologies of diagnostic radiology provide an opportunity to determine ischemic territories and patterns of deficient cerebral perfusion [Jauch et al., 2013]. Perfusion CT and MR are a functional imaging methods, that combined with up to date examination protocols, provide significant complementary data on vascularization, perfusion and function of the brain tissue. [Mullins et al., 2006].

If an acute cerebral ischemic stroke is diagnosed early within 3 to 4.5 hours and a viable area of brain tissue is detected by means of multimodal CT and MR techniques, there is an opportunity to use selective and differential therapeutic strategies: where applicable, active pathogenetic treatment, i.e. intravenous or intraarterial thrombolysis, or thrombectomy [Martin-Schild et al., 2009, Yu et al., 2009]. The parts of the brain with adequate perfusion are assumed to be relatively protected from ischemia and infarction, whereas those

with impaired cerebral hemodynamics and insufficient collateral blood supply have a higher risk of ischemia and infarction [Caplan et al., 2006]. Insufficient collateral blood supply may result in critically low cerebral blood flow and cause irreversible tissue lesion (core zone). The potentially viable area of the brain tissue surrounding necrosis is called penumbra. By means of functional imaging techniques such as perfusion CT and additional measurements it is possible to evaluate the status of ischemic brain areas and the collateral blood flow [van Laar et al., 2008]. Perfusion CT data are sufficiently compatible with MR examination findings, and it is a faster and a more accessible examination than MR [Jauch et al., 2013].

Cerebral infarction study data concerning the evaluation strategy and the algorithm of acute ischemic stroke, and the assessment of cerebral hemodynamics in the perfusion CT are rather variable and hardly comparable [Mullins et al., 2006; Kim et al., 2011; Kidwell et al., 2013; Broderick et al., 2013]; this study has produced new data on the ability of the CT perfusion to distinguish reversible and irreversible lesions in the brain tissue by use of multimodal examination protocol. The most relevant thresholds of measurements have been established which can be used as early possible markers in predicting clinical outcomes.

No sufficient research has been conducted to date for patients with acute cerebral ischemic stroke and atherosclerotic changes in brachiocephalic blood vessels and the association of these changes with cerebral perfusion in acute cerebral ischemic stroke [Rothwell et al., 2008]. Our study has resulted in new data on the association of blood vessel atherosclerosis with the location of blood vessel occlusion, collateral blood supply of the brain, and the grade, extent and outcome of the ischemic lesion.

Elaborated protocol for the assessment of cerebral perfusion in the case of acute cerebral ischemic stroke during this study provides an opportunity to improve the precision of radiological diagnostics and facilitates the selection of the most appropriate treatment strategy thus improving the quality of the patient's life.

The structure of the doctoral thesis:

Doctoral thesis is written in latvian and executed on 160 pages. It has 3 attachments. The work has a classic design, it includes annotations in Latvian and English, introduction, topicality, novelty and practical significance of the study, the aim and the objectives of the study, hypothesis, literature review, materials and methods, results, discussion, conclusions, list of publications and reports, bibliography which includes 187 references. Doctoral thesis contains 19 tables and 39 figures.

The aim of the study was to:

To characterize brain perfusion in acute cerebral ischemic stroke with and without atherosclerotic changes in brachiocephalic blood vessels, using multimodal computed tomography examnination, and to determine the role of imaging in the diagnostic algorithm and the selection of therapy.

Study objectives:

1. Develop and approve the multimodal CT examination protocol and perfusion methodology for acute ischemic stroke patients.
2. Collect imaging data and analyse brain perfusion hemodynamics parameters according to alteration in extra- and intracranial blood vessels and collateral blood supply.
3. Determine perfusion CT parameter threshold values in definition and charaterization of ischemic lesion type, grade, location and size.
4. Analyse value of perfusion CT data and collateral blood supply in prediction of possible clinical outcome.

Hypotheses:

1. Necrosis and penumbra extent in acute cerebral ischemic stroke patients with or without atherosclerotic changes in brachiocephalic blood

vessels is different, necrosis extent correlates to stenosis grade and occlusion location.

2. Marked functional collateral network is seen in patients with chronic intracranial circulation impairment due to atherosclerotic changes in brachiocephalic vessels, and increased reperfusion through existing collaterals correlates to favorable outcome.

Topicality, novelty and practical importance of the study:

1. This is the first study in Latvia on capabilities of multimodal computed tomography (CT) examination protocol in diagnostics of acute cerebral ischemic stroke, by combining the non-enhanced brain CT, CT angiography and CT perfusion methods.
2. The methodology of multimodal CT protocol has been approbated in a clinical practice. Recommendations have been developed for examinations to facilitate early acute cerebral ischemic stroke diagnostics in clinical practice.
3. The study resulted in new data on the capability of CT perfusion to recognize the brain tissue with reversible and irreversible ischemic lesions. The most relevant measurement thresholds have been defined, that can be used as markers in prediction of clinical outcomes.
4. This study has resulted in new data on the association of blood vessel atherosclerosis with the localization of blood vessel occlusion, collateral blood supply of the brain, and grade, extent and outcome of the ischemic lesion.
5. The protocol of assessment of cerebral perfusion developed during this study provides an opportunity to improve the precision of radiological diagnostics in acute cerebral ischemic stroke and facilitates the possible selection of the most appropriate treatment strategy thus improving the quality of the patient's life.

Personal contribution

The author personally participated in all stages of the research – in the study design, in the collection of data, computed tomography examination and data post-processing, statistical analysis, interpretation of the results obtained, literature review, preparation of publications, theses, conferences reports, and translation. She is also the author of the published images.

This combined (cross-sectional prospective and group-control retrospective) study was approved by the Ethics Committee at Riga Stradins University and the Scientific Department at Pauls Stradins Clinical University Hospital.

1. MATERIAL AND METHODS

1.1. Patient selection

The study analyses 297 patients who underwent 306 multimodal examinations of computed tomography during the period June 2011 to December 2012. Patients included in the study had acute neurological deficits corresponding to cerebral infarction (CI or acute cerebral ischemic stroke) and they have been admitted to the Emergency Department of Pauls Stradins Clinical University Hospital or developed their symptoms during their stay at the hospital. Each multimodal examination was treated as a single event, including recurrent CI during the study period.

1.1.1. Study inclusion criteria

The patients included in the study had clinical and radiological criteria characteristic of acute cerebral ischemic stroke:

1) clinical criteria (sudden neurological deficits characteristic of acute cerebral ischemic stroke (with hemisyndrome, impaired speech, vision, coordination etc.)) during the phase of acute admission or hospital stay regardless of gender and age within 6 hours since onset of the symptoms, and also patients with unknown onset of the symptoms or so called “wake-up” stroke (if the patient has no symptoms of neurological deficits before the night sleep). The study includes patients with the neurological status score NIHSS ≥ 1.
2) radiological criteria: a qualitative multimodal CT examination has been performed and a quantitative postprocessing of high resolution images by an automated computing software is possible.

1.1.2. Study exclusion criteria

1. Radiological criteria: signs of intracerebral hemorrhage in the non-enhanced brain CT.
2. Technically inconclusive images due to patient hemodynamics (heart rhythm disorders, blood pressure fluctuations) or motion artifacts.
3. Clinical-neurological symptoms that resolve within 24 hours since the onset indicating a transient ischemic attack (TIA). Clinical, laboratory or radiological exclusion of a territory acute cerebral infarction or confirmation of other pathology which can mimic the neurological deficiency of cerebral infarction (e.g., decompensation symptoms after CI in the localization corresponding to clinical symptoms, tumor, metastasis, neurodegenerative disease etc.) [Keedy et al., 2012].

Clinical data on the treatment (standard treatment, thrombolysis or mechanical thrombectomy) and the outcome were obtained in collaboration with the Neurology Clinic of Pauls Stradins Clinical University Hospital and were based on the patients records and medical history documents accessed at the Medical Archive of Pauls Stradins Clinical University Hospital.

After analysis of the medical documentation of 306 cases, **229 cases with clinically and radiologically confirmed cerebral infarction (CI) were selected**. Patients excluded from the study were diagnosed as follows: 30 patients had other pathology, 26 patients had transient ischemic attack (TIA), which was initially assessed as a neurological deficiency in the anterior circulation territory, and 5 patients had previous CI and presented with symptomatic decompensation, as well as 16 cases of erroneous examinations. 119 (52%) of selected 229 patients were female and 110 (48%) were male between the age of 28 and 87 (mean age 69.85±11.14 years). The period from the onset of the symptoms to the examination varied from 40 to 510 minutes or 1 to 9 hours (mean time 247.03 minutes ± 157.25). The analysis of radiological images demonstrates the involvement of the anterior circulation territory (mostly MCA) in the majority of cases, 184 cases or 80.34%, the involvement of the posterior (vertebrobasilar) circulation territory (VBT) in 40 cases or

17.46% and the involvement of other territories (borderzone territories) in 5 cases or 2.18%. Distribution of patients by CI subtypes is shown in table (Table 1.1.).

Table 1.1.

Distribution of patients by subtypes of CI by TOAST criteria*

TOAST classification CI	Number of patients		Age		Gender				Territory		
	N	%	Mean	SD	female		male		MCA	VBT	other
					N	%	N	%			
Cardioembolic genesis	104	45.4	70	10	57	47.9	47	42.7	85	15	4
Atherothrombotic genesis	69	30.1	68	11	36	30.3	33	30.0	58	11	0
Small blood vessel pathology	22	9.6	69	12	10	8.4	12	10.9	17	5	0
Unspecified etiology	25	10.9	70	13	13	10.9	12	10.9	19	6	0
Other cause	9	3.9	67	12	3	2.5	6	5.5	5	3	1
Total	**229**	**100**	**-**	**-**	**119**	**100**	**110**	**100**	**184**	**40**	**5**

SD=standard deviation; * - adapted from Adams et al., 1993.

1.1.3. Study and control group

The patients with acute cerebral ischemic stroke were **divided into two main groups** according to the presence or absence of atherosclerotic changes in the CT angiography:

1) The study group (with atherosclerosis) includes patients with radiologically detected atherosclerotic-stenotic changes in extracranial blood vessels (n=170).

2) The control group (without atherosclerosis) includes patients without radiological finding of atherosclerotic-stenotic changes in the extracranial blood vessels (n=59).

For the stages and criteria of patient selection see the figure below (Figure 1.1).

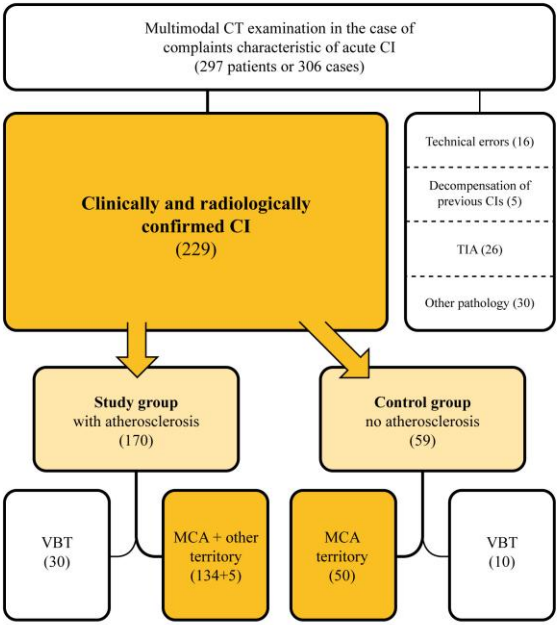

Figure 1.1. Selection criteria and allocation of examined patients into groups

By the selective criterion – atherosclerosis from all approved CI cases (n=229) – we found 169 cases or 73.79% with atherosclerosis (ACM and other blood supply territory - 139, VBT - 30), while the control group without atherosclerosis by CT angiography (CTA) findings were 60 cases or 26.20% (anterior circulation territory - 50, posterior circulation territory - 10). Since the posterior circulation territory CI cases (n=40) were a small number in the study (n=30) and control group (n=10) of patients by criterion atherosclerosis and additional parameter - collateral blood supply was poorly interpretable in this territory, those patients were excluded from further analysis in order to obtain a more homogeneous composition of the selected group to perform statistical analysis and correlation of parameters.

The group of anterior circulatory territory CI **(MCA territory)** comprised **189 cases**. **139** (73%) of 189 cases were included in the

atherosclerosis or **study group,** whereas **50 cases** (27%) were included in the group without atherosclerosis or **the control group**. Among selected cases were 14 lethal outcome cases.

A patient data base was created, using *Microsoft Office Excel* program.

1.2. Multimodal computed tomography examination protocol

The choice of the multimodal CT examination for the primary radiological diagnostics of acute cerebral ischemic stroke patients was based on the following aspects: availability of the CT method for 24 hours a day, 7 days a week and suitability of the examination in terms of the obtained information for extended radiological diagnostics of acute cerebral ischemic stroke patients. All study patients in acute stage underwent 3 subsequent series of CT imaging with 64-row multislice computed tomography device *General Electric Light Speed VCT XT 64*. Non-enhanced brain CT (NCT), CT angiography (CTA), CT perfusion (CTP), after assessment of clinical data and clarification of onset time. Follow-up imaging was performed after 24 hours or later, after evaluation of clinical indications. Non-enhanced CT (NCT) was used as the main method to exclude cases of intracerebral hemorrhage and other pathology mimicking the clinical symptoms of acute cerebral ischemic stroke from the study [Ledezma et al., 2009, Gelfand et al., 2010]. If no hemorrhage or signs of other pathologies were detected in non-enhanced brain CT (NCT), or if there were indirect signs of acute ishemia, the examination was continued using a multimodal protocol with CT angiography and CT perfusion. CT angiography was performed from the aortic arch up to the vertex in the axial plane, including both extracranial and intracranial blood vessels after an intravenous (i.v.) bolus administration of iodinated non-ionic contrast media. The examination was followed by a perfusion CT series, including the blood vessels of the circle of Willis. A series of dynamic contrast with a scanning area of 4 cm was performed after i.v. administration of iodinated contrast media slightly above the level of skull base. Repeated scanning of the marked area through the entire contrast phase of 50 seconds resulted in 712 images comprising 8 levels.

The total time of the multimodal CT examination was 4 to 40 minutes (mean 10 minutes (SD=25)). As the patients movements during examination are a significant obstacle in acquisition of CTA and CTP series, fixation of the examination area (head) for all patients was done.

1.2.1. Postprocessing of radiological data

The postprocessing of the acquired brain perfusion and angiography data was performed in the specialized work station *GE Advantage Workstation, version 4.4* using standardized automated processing software application *CT Perfusion, version 4*.

The postprocessing of CT angiography series assessed the source axial images and additionally multiplanar reconstructions in the sagital, axial and coronar planes. The following 2-dimensional and 3-dimensional evaluation of blood vessels was performed (Figure 1.2).

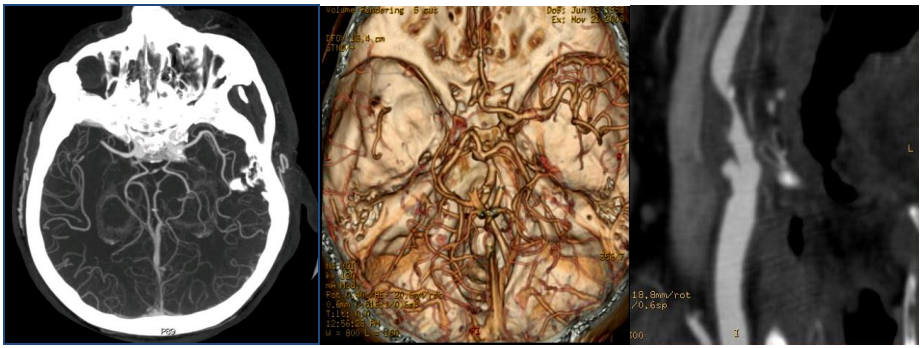

Figure 1.2. Reconstructions of CT angiography images*.

A – MIP reconstructions of the intracranial blood vessels, occlusion of right proximal MCA with good collaterals, B – Volume rendering (VR) of the intracranial blood vessels, C – Curved reformat (CR), suboclusion of right internal carotid artery.
* Images of the study patients from the author's archive.

The anatomy, course and alteration of lumen of the intracranial and extracranial blood vessels were assessed. Intracranial assessments: stenoses and occlusions were evaluated according to clinical symptoms and localization of changes by indicating the name of the blood vessel and the affected segments.

Intracranial collaterals were assessed and divided into 3 subtypes: 1 – malignant collaterals (marked absence of leptomeningeal collateral blood vessels or inability to differentiate them in the respective hemisphere affected by CI), 2 – Poor (the collaterals are seen in <50% of the blood supply territory), 3 – Good (slight asymmetry of the collaterals, collaterals are seen in >50% of the blood supply territory); this classification was adapted from other authors publications [Tan et al., 2007; Souza et al., 2012].

The analysis of the final results was carried out by comparing atherosclerotic changes in brachiocephalic blood vessels and status of collateral blood flow. Extracranial assessments: stenoses, occlusions, atherosclerotic plaques with a localization, detection of changed unit of the blood vessel and the affected segments were defined by internationaly known methodology by NASCET [Allan et al., 1993; NASCET collaborators, 1991] (according to the decrease of lumen diameter compared to the distal segment), the grade of stenosis were classified in 4 groups according to percentage of stenosis: 1) up to 49% mild stenosis; 2) 50-69% moderate stenosis; 3) 70-99% severe stenosis, subocclusion; 4) 100% or occlusion. For the subtypes of collaterals please refer to the figure (Figure 1.3). Collateral evaluation was not performed at posterior circulation territory.

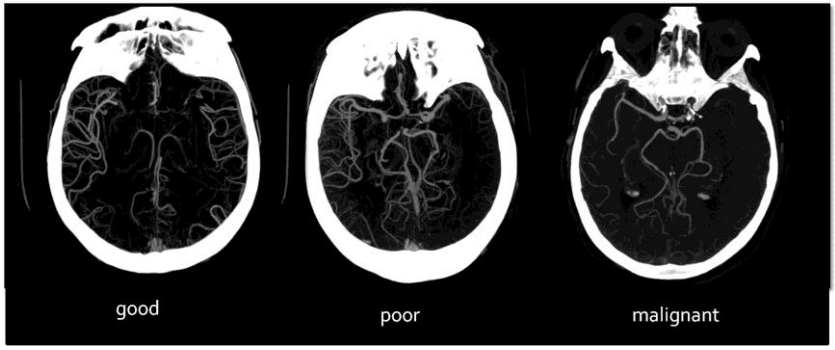

Figure 1.3. Subtypes of intracranial collaterals. CTA MIP images, intracranial blood vessels. Occlusion of segment M1/M2 of left middle cerebral artery
Image on the left – good collaterals in the left hemisphere; image in the middle – poor collaterals in the left hemisphere; image on the right – absence of collaterals in the left hemisphere (malignant). * Images of the study patients from the author's archive.

1.2.2. Computed tomography perfusion analysis

The postprocessing of CT perfusion images was carried out using standardized deconvolution calculation software, *CT perfusion, version 4.0* [Wintermark, 2005]. The system automatically offers automated intracranial reference blood vessels for calculations: an artery (usually – *A. cerebri anterior*) and a vein (*sinus sagittalis superior* or *transversus*) (Figure 1.4, b). If the automated blood vessel selection was done incorrectly it was possible to correct it manually.

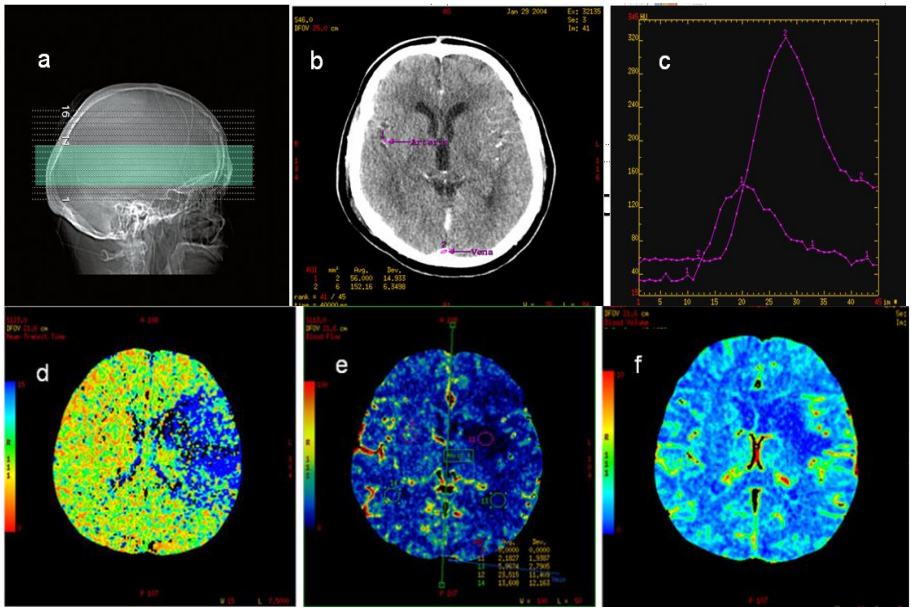

Figure 1.4. Postprocessing of CT perfusion data*.

S, 52 years old with a left-sided hemiparesis. a – examination area, b, c – dynamic contrast-enhanced curve of reference blood vessels (artery, vein), d, e, f – perfusion maps, CT perfusion maps: d – MTT, e – CBF, f – CBV. Hypoperfusion in the left parietal lobe. In the region of basal nuclei the perfusion defect match in CBF (e) and CBV (f) maps, i.e. the core zone. In the MTT map (d), the larger perfusion deficiency zone around the core zone is a potentially reversible penumbra lesion. In the images d, e, f, quantitative measurements of the core and penumbra zones in the left hemisphere and identical measurements in the contralateral hemisphere. * Images of the study patients from the author's archive.

Following the generation of a dynamic contrast-enhanced curve (Figure 1.4. c) of the reference blood vessel (Figure 1.4, b) it was possible to generate perfusion maps for 3 main parameters: cerebral blood flow mL/min/100 g (CBF), cerebral blood volume mL/100 g (CBV) and mean transit time (MTT), reproduction of cerebral perfusion in color see figure (Figure 1.4. d,e,f).

If a visual defect was identified in all 3 maps, it was defined as a necrosis or irreversible lesion, i.e. core lesion; if the area of pathology matched in both CBF and CBV maps, it indicated necrotic lesion. If the deficiency in MTT and CBF maps did not matched with CBV map, it was classified as a potentially reversible lesion, i.e. penumbra lesion [Ledezma et al., 2009; Wintermark et al., 2006, 2008]. Then quantitative measurements were performed comparing the extent of lesion. Absolute and relative measurement quantitative parameters of cerebral perfusion in all 3 maps were obtained by applying a region of interest (ROI) in different locations of the zone of perfusion deficiency, adjusting the midline and placing identical ROI in the contralateral hemisphere [Leiva-Salinas et al., 2011]. Quantitative measurements were defined a percentage relative to normal parenchyma which was assumed to be 100% (decreased <100%, increased >100%).

The CT perfusion changes were evaluated according to neurological status (NIHSS and mRS score) and CT angiography findings in extracranial and intracranial blood vessels: the location of an acute blood vessel occlusion, the location of a stenotic defect in the extracranial blood vessels, the degree of stenosis and collateral blood supply.

1.2.3. Assessment of stroke volume in the CT

The core and penumbra zones were defined as a result of visual and quantitative CTP analysis. The localization and volume of the lesion was defined according to the ASPECTS score (Alberta Stroke Program **Early CT Score**) [Aviv et al., 2007]. The final assessment was done by the localization of the core zone using the ASPECTS score, where normal findings corresponded

to 10 points. 9 points corresponded to a single localization of the core, 0 points corresponded to the total lesion of the hemisphere, respectively (Fig.1.5).

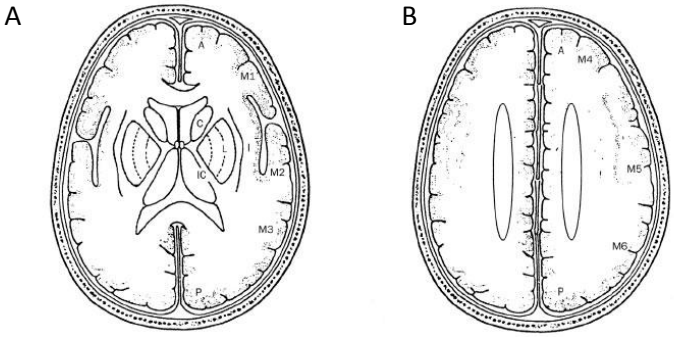

Figure 1.5. Scheme of a quantitative topographic CT scan score (ASPECTS)

A - The level at the basal ganglia. B - The level above the basal ganglia. A – Anterior, C – *Caudatus*, I – Insula, IC – *Capsula interna*, L – *Nucleus Lentiformae*, M1 – Anterior cortex of MCA, M2 – Lateral cortex of MCA, M3 – Posterior cortex of MCA, M4, M5, M6 represent the anterior, lateral and posterior cortex of MCA just above M1, M2 and M3, rostrally against the basal ganglia. Subcortical structures create 3 points (C, L and IC). The cortex of MCA creates 7 points (insula, M1, M2, M3, M4, M5 and M6). The figure is adapted from Aviv RI et al., 2007.

CTP ASPECTS were reassessed after follow up examination.

1.2.4. Follow-up radiological examinations

In all study patients with a confirmed CI who underwent intravenous thrombolysis or mechanical thrombectomy a follow-up NCT was performed within 24 hours. Similarly, the patients with deterioration of the neurological status (including complications) or marked clinical presentation and negative or technically erroneous finding in CT perfusion underwent follow-up radiological CT (n=186) or MR (n=15) examinations. The data of follow-up radiological examinations were retrospectively compared to the initial CT perfusion findings, and the volume of lesion was repeatedly assessed by the ASPECTS score (n=146).

In patients with focal symptoms who did not required repeated NCT according to the clinical presentation in the hospitalization phase (n=14) and in patients with a lethal outcome (n=14) the clinical result was assessed retrospectively based on the information in medical records without an additional follow-up examination.

1.3. Statistical analysis of the data

Microsoft Office Excel 2007 program was used for data collection in patient database. For statistical analysis of data *IBM SPSS version 19.0* and *Graph Pad Prism* program *version 5.01* were used. Statistical methods of data analysis:

1. Descriptive statistics - to calculate the indicators of central tendency (mean, median, mode) and dispersion parameters (standard deviation), minimum and maximum values were evaluated. The Kolmogorov-Smirnov test was used to determine if the data had normal distribution ($p>0.05$) or not normal distribution ($p<0.05$). Conclusive statistics: hypothesis testing methods, group comparison, which was performed for independent variables using univariate ANOVA (one-way Analysis of Variance) test and Pearson chi-square test. To compare two dependent groups appropriate t-test or Wilcoxon signed rank test were used to identify differences between related pairs, as well as non-parametric Mann-Whitney U or Kruskal-Wallis test were performed.

2. To correlate two variables comparative methods were used as well as multi-variable correlation methods (Spearman and Pearson correlation). In the research the following correlation classification was used according to the size of the correlation coefficient r: correlation is weak if $r \leq 0.3$, correlation is medium when $r\ 0.3 < r < 0.7$, but strong correlation if $r \geq 0,7$.

3. ROC (Receiver Operating Characteristic) curve was used to detect method sensitivity and specificity and threshold values. To compare the quality of test - area under the curve (AUC) was used. In order to generalize the results and determine the dispersion limits were also calculated 95% confidence

interval values. Area under curve AUC <0.8 correspond to weak result, 0.8-0.9 to good result and AUC> 0.9 – to an excellent result for diagnostic test [Zhu et al., 2010]. Correlation among multiple parameters and clinical outcome was assessed by building logistic regression model. For comparison of coincidence between CT perfusion results interpretation between two interpreters (radiologists) Cohen's kappa analysis was used.

2. RESULTS

After post-processing of image data from multimodal CT examination of 297 patients, 2391 brain perfusion parameter measurements were made in the defined areas of interest: 708 in the irreversible ischemic zone, 810 in the tissue at risk or penumbra zone and 873 measurements in normal brain matter. 1224 extracranial blood vessels evaluated.

2.1. Atherosclerosis

After CTA image analysis in anterior circulation territory CI (n=189) between research and control group based on Pearson's chi-square statistical analysis we revealed statistically significant difference among age groups (p=0.025), but no significant differences by gender were observed (p=0.4). Atherosclerosis trend is more observed in the age group over 50 years (70.90%), whereas the number of patients without atherosclerosis was 1.6 times smaller in the age group above 75 years (8.99%) compared to the age group of 50-69 years (14.29%).

2.1.1. Stenotic changes in extracranial blood vessels

Changes in extracranial blood vessels in study group were further analyzed in anterior circulation territory (n=129), estimating stenosis degree, based on the internationally accepted classification of NASCET: at internal carotid artery (ICA). The extracranial part was classified into mild degree of stenosis (up to 49%) in 70 patients or 50.4%, moderate degree stenosis (50-69%) in 14 patients or 10.1%, severe stenosis (70-99%) in 11 patients or 31.7% and total occlusion of the lumen in 44 patients or 31.7%.

To specify the relationship between atherosclerotic changes and acute cerebral ischemic stroke (CI) subtype (by TOAST classification), it was found that in extracranial vascular stenosis group (up to 49%) patients had tendency to cardioembolic etiology (n=42) CI subtype and small vessel occlusion (n=10)

CI subtype, while the occlusion group – to atherothrombotic type (n=38). In control group without atherosclerosis most often cardioembolic etiology CI type was seen (n=34) as well as stroke with undetermined etiology (n=12). CI caused by other determined etiology was found only in the moderate stenosis group (n=3) and in the control group (n=3) (Table 2.1.).

Table 2.1.

Cerebral ischemic etiology subtypes in study groups (by TOAST classification)

	Count(n)	CI etiology subtype				
		small vessel	athero-thrombotic	cardio-embolic	undetermined cause	other cause
No atherosclerosis	50	1 (2%)	0	34 (68%)	12 (24%)	3 (6%)
>49%	70	10 (14.3%)	11 (15.7%)	42 (60%)	4 (5.7%)	3 (4,3%)
50-69%	14	3 (21.4%)	4 (28.6%)	6 (42.9%)	1 (7.1%)	-
70-99%	11	1 (9.1%)	5 (45.5%)	4 (36.4%)	1 (9.1%)	-
100%	44	2 (4.5%)	38 (86.4%)	3 (6.8%)	1 (2.3%)	-
Total	189	17 (9%)	58 (30.7%)	89 (47.1%)	19 (10.1%)	6 (3.2%)

Extracranial vessel stenosis groups (up to 99%) patients had statistically significantly favorable outcome (p=0.001) in comparison to cases of internal carotid artery occlusion, where equal quantities of favorable outcome (n=21) and adverse outcome (n=23) (p=0.6) were obtained.

2.1.2. Stenotic changes in intracranial blood vessels

Intracranial vascular stenotic changes were found in 143 (75.6%) cases out of 189. Middle cerebral artery (MCA) lumen diameter stenosis by visual assessment of CTA images were divided into groups by local lumen narrowing – up to 50%, 50-69% and 70-99% stenoses groups. Since within those groups a small number of patients was observed and only good collateral subtype was present, they were merged into a single stenosis group up to 99% (n=21). Artery occlusion was found in 125 cases and no evidence of pathology in 46 cases.

For evaluation of intracranial stenosis incidence within study group with atherosclerotic changes in extracranial blood vessels and control group, no statistically significant difference was observed (p=0,51).

In order to thoroughly assess acute changes in intracranial and extracranial vessels caused by atherosclerosis the location of the occlusion was analyzed.

2.1.3. Acute occlusion location in blood vessels

Analyzing acute vascular occlusion location was defined in following subtypes: *a. cerebri media* (MCA) proximal occlusion at M1 segment (n=28), distal at M2 segment (n=84), *a.carotis interna* (ICA) extracranial part proximal site (n=10) or total ICA and MCA proximal occlusion (n=24). Vascular occlusion site could not be identified in 43 cases on CTA images.

There was no statistically significant difference revealed by gender, age and hemisphere among the locations of the vessel occlusion ($p>0.05$).

In general, of all intracranial occlusion, the most frequent location was observed in ACM M2 segment (n=63) that was more often found in patients with mild (>49%) and moderate (50-69%) extracranial stenosis ($p<0.0001$), which can be associated with cardioembolic etiology CI type (n=48, 76.2%) and to a lesser extent with atherothrombotic etiology CI type (n=15, 23.8%).

Using the Spearman correlation test, a statistically significant correlation was found between the **occlusion site and collateral type** ($r=-0.33$, $p<0.0001$), from that we concluded that wider or more proximal occlusion segments corresponded to less collaterals.

In cases of ACM M1 proximal segment occlusion about half of the patients (n=15) had good collaterals and one in five patients (n=6) had malignant collaterals. Most cases of peripheral type ACM M2 segment occlusions showed good collaterals.

In the case of combination of ICA and MCA occlusion collaterals were generally poor (n=10, 42%) and malignant (n=6, 25%); only 30% had good collaterals (n=8), while the largest proportion of malignant collaterals

30% was in the cases of ACI proximal occlusion (n=3), ($p<0.0001$). The results are summarized in table (Table 2.2.).

Table 2.2.

Characterization of occlusion site and collateral blood supply

Occlusion site	Count (n)	Collateral blood supply subtype		
		malignant	poor	good
No occlusion	43	-	-	43 (100%)
M1 segment	28	6 (21.4%)	7 (25%)	15 (53.6%)
M2 segment	63	2 (3.5%)	15 (23%)	46 (73.5%)
ICA	10	3 (30%)	1 (10%)	6 (60%)
ICA+MCA	24	6 (25%)	10 (41.7%)	8 (33.3%)
Total	168	17 (10.1%)	35 (19.6%)	118 (70.3%)

Intracranial occlusion correlates with the size of CT perfusion defect or ASPECTS scale score assessment at admission and ASPECTS in follow-up imaging ($r_s=0.47$, $p<0.0001$ and $r_s=0.37$, $p<0.0001$). ASPECTS scale threshold value 7 was used to define favorable (≥ 7) and unfavorable (<7) outcome.

In the case of ACM M1 segment or ICA proximal occlusion ASPECTS score mean values were between 6 and 7, which correspond to unfavorable clinical outcome – correlation was weak and statistically significant ($r_s=0.33$, $p<0.0001$). However, for group without intracranial occlusion ASPECTS scale score was over 9 and in the case of M2 segment occlusion - above 8, which correlates with a good outcome. This was moderately strong correlated and statistically significant ($r_s=0.53$, $p<0.0001$).

Also, the occlusion site had weak, but reliable relation with apparent core or necrosis lesion size on CT perfusion images ($r_s=0.25$, $p=0.0001$), but the penumbra area or potentially reversible lesion size and outcome defect size in follow-up examinations did not statistically significantly correlate with occlusion site ($p=0.67$ and $p=0.2$). From this we concluded that the primary visible penumbra area in CT perfusion later changes independently from occlusion site. All above data correlation was performed using Spearman

correlation test, because the analyzed data were non-normally distributed, by the Kolmogorov-Smirnov test ($p<0.05$).

Kruskal-Wallis test did not showed a reliable difference between the occlusion site and relative CT perfusion parameters ($p>0.05$).

A statistically significant correlation was observed between occlusion site and final neurological scales NIHSS score ($r_s=0.18$, $p=0.01$) and mRS score ($r_s=0.14$, $p=0.04$). There were more patients with ICA and MCA combined occlusion and with severe neurological deficit (mRS score 5) or lethal outcome (14 out of 25 patients), and at the M2 segment occlusion there were more patients with moderate mRS score - 4 points (18 out of 83 patients).

9 patients from lethal cases had hemorrhagic complications at the acute ischemic site of the brain, that corresponded to the ICA proximal occlusion (n=5) or MCA and ICA combined occlusion (n=4). Retrospectively analyzed CT angiography and CT perfusion source images for patients with hemorrhagic complications showed an extravasation pattern of contrast media locally in the brain tissue.

2.2. Collateral blood supply of the brain

Assessing collateral proportion in the brain during event of acute cerebral ischemic stroke (CI), they were divided into three subtypes - malignant, poor and good. For patients with posterior circulation territory CI this parameter was not evaluated during this study. For comparison of atherosclerosis and control groups territory CI cases statistically significant difference between the distribution of collateral types between study and control groups was not found ($p>0.05$), but in detailed assessment of extracranial vascular stenosis groups we obtained a relationship between stenotic changes and collateral subtype. Malignant collaterals (n=11; 20%) were found the most in the group with severe stenosis > 70% and were not detected in the moderate stenosis group. Poor and good collaterals were found in all stenoses groups, with no statistically significant difference ($p>0.05$), but in the mild stenosis group (up to 49%) we observed a trend towards good

collaterals, in comparison with other collateral subtypes (malignant n=4 (5, 7%), poor n=9 (12.9%), good n=57 (81.4%)). Results are summarized in table (Table 2.3.).

Table 2.3.

Collateral subtypes in the study and control groups

		Collateral blood supply subtypes		
Study groups	**Count (n)**	**malignant**	**poor**	**good**
No atherosclerosis	50	2 (4%)	10 (20%)	38 (76%)
Atherosclerosis	139	15 (10.8%)	25 (18%)	99 (71.2%)
Grade of ICA proximal stenosis				
<49%	70	4 (5.7%)	9 (12.9%)	57 (81.4%)
50-69%	14	-	4 (28.6%)	10 (71.4%)
>70%	55	11 (20%)	12 (21.8%)	32 (58.2%)
Total	189	17 (9%)	35 (18.5%)	137 (72.5%)

Collateral and intracranial vascular stenotic changes were evaluated using Pearson's chi-square test and a statistically significant relationship was found between the parameters of the data (p=0.003). Based on Cochran-Mantel-Haenszel test the odds ratio of good collaterals in cases of intracranial stenosis for patients without atherosclerosis (OR=12.88) and in the atherosclerosis group (OR=15.48), however no statistically significant relation was found (p>0.05).

When we correlated collateral types to ASPECTS score at admission, that shows the extent of the ischemic core, we found that there was a statistically significant moderate correlation between good collaterals and smaller core lesion (r_s=-0.59; p<0.0001). Likewise the same approach could be used for correlation with admission NIHSS lower score in presence of good collaterals at admission (r_s=-0.47; p<0,0001) and discharge (r_s=-0,46; p<0,0001).

2.3. Perfusion lesion type and grade

Perfusion defect evaluation of CT perfusion maps determined lesion types - isolated or combined lesion and lesion. Lesions were also divided by grade - irreversible or reversible type ischemic lesion. CTP maps with normal findings were found in 43 (23%) out of 189 cases and pathological findings in 146 (77%) cases; from those an isolated or **"core" lesion** was found in 29 (15.30%) cases (match of lesion area in CBV and CBF maps). An isolated reversible type or **penumbra lesion** was found in 41 (21.70%) cases (mismatch between CBV and CBF maps). **Combined core and penumbra lesions** were found in 76 (40.2%) cases.

The standard radiological signs of CT perfusion defects obtained in the study are shown in the figure (Figure 2.1.) where the color images represent CT perfusion maps and the grayscale images - baseline CT.

The differences were found during assessment of **collateral type and combination of CT perfusion defects** (isolated penumbra, core lesion or combined lesion); they showed significant differences ($p<0.0001$). The results are summarized in table (Table 2.4.).

Table 2.4.

CT perfusion lesion type and degree distribution by collateral blood supply subtypes

Perfusion lesion type and grade		Collateral blood supply subtypes		
	Count (n)	malignant	poor	good
Isolated Core	29	9 (31%)	9 (31%)	11 (38%)
Isolated Penumbra	41	-	4 (10%)	37 (90%)
Penumbra +Core combination	76	8 (10%)	22 (29%)	46 (61%)
Total	146	17 (11,8%)	35 (24,3%)	94 (63,9%)

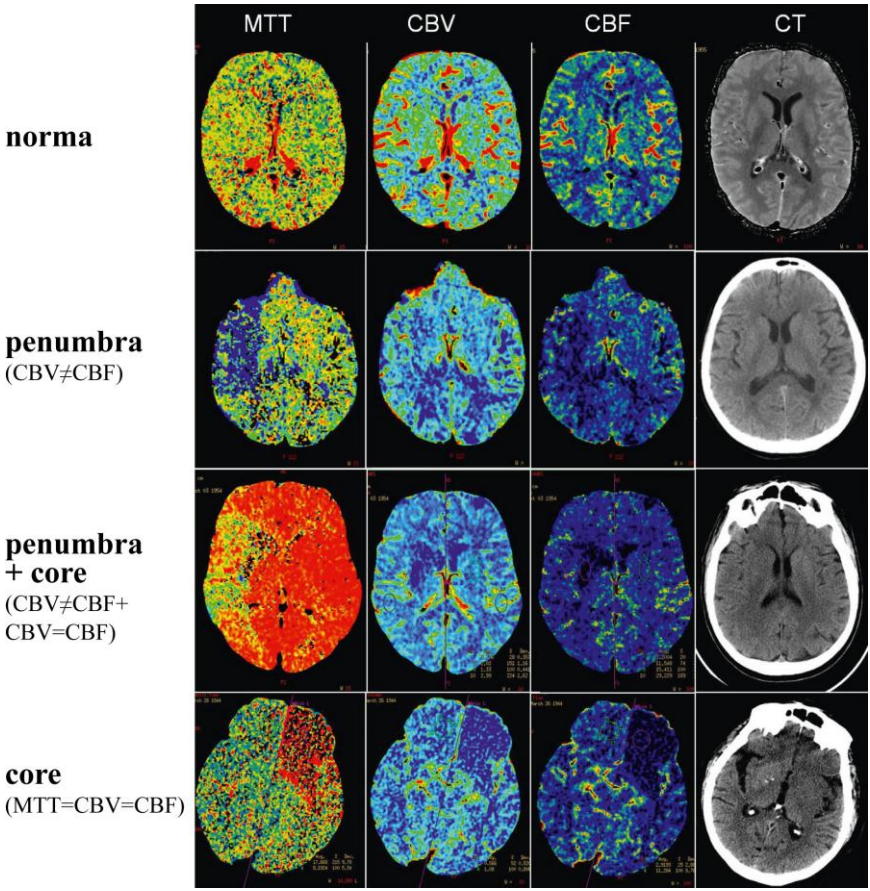

Figure 2.1. Types of cerebral perfusion deficiency in the CTP maps and the comparison with findings in non-contrast CT.

Normal findings (the top row); penumbra (the 2nd row), the defect in the MTT map and to a lesser extent in the CBF map, not seen in the CBV map; combined penumbra (in the right hemisphere) and the core (in the basal ganglia of the right hemisphere) (the 3rd row); only the core (the bottom row), the defect is seen in all 3 maps. In the 3rd and 4th row, comparative quantitative measurements in the affected zone and healthy hemisphere were done.

* Images of the study patients from the author's archive

This finding suggests relationship between collateral types and the degree of perfusion lesion - an isolated penumbra lesion associates with good collaterals and a core isolated lesion or combined lesion associates with poor or malignant collaterals, although the Spearman correlation test results were not statistically significant (p=0.6).

2.4. Perfusion lesion localization and extent

Additionally analyzing **acute cerebral ischemic stroke localization and extent** in anterior circulation territory (n=189) in CT perfusion image changes were divided into groups: 1) affected only the basal ganglia, 2) only hemispheric sectoral lesion 3) the combination of basal ganglia and hemispheric sectoral lesion 4) extensive hemisphere lesion. The core type lesion was observed in all groups.

Assesing the extent of **penumbra type lesion**, it was detected in 117 out of 189 patients (62%) and mostly as a partial hemispheric ischemia. 10 cases of identified penumbra lesion were false positive and associated with chronic internal carotid artery proximal subocclusion-occlusion or in 7 cases an anatomical variation of intracranial blood vessels.

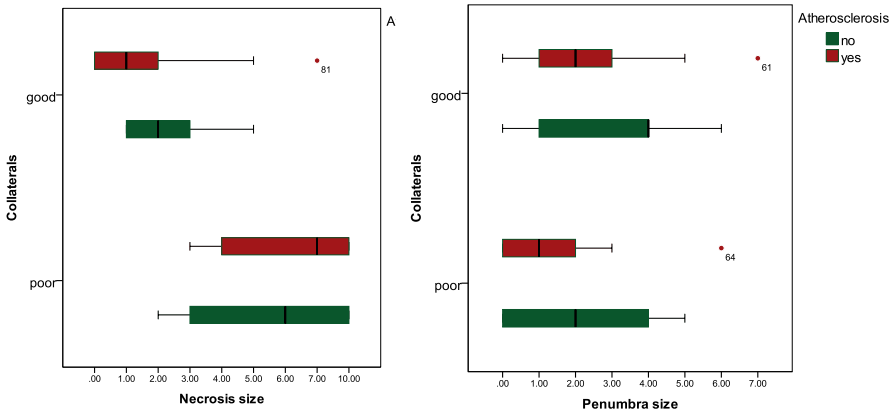

Figure 2.2. Penumbra and necrosis extent correlation to collateral subtypes.

Core type lesion was found in 105 out of 189 CI patients (55%). Isolated core lesion type mostly affected sectoral hemisphere gray and white matter or created an extensive hemispheric lesion. There was statistically significant difference ($p<0.0001$) between the groups.

The size of the lesion was defined using ASPECTS score in the 10-point scale, differentiating lesion extent in penumbra and core locations, where the smaller number of involved areas means less extent.

We compared necrosis and penumbra extent and collaterals. By the criterion atherosclerosis, the necrosis area showed statistically significant difference ($p<0.007$) - good collaterals correlated with a small amount of necrosis ($r_{s=}0.6$, $p<0.0001$), while in the cases of poor collaterals and absence of atherosclerotic changes a more extensive necrotic lesion (from 3 to 10 units) ($r_s=0.6$, $p=0.01$). Good collateral proportion weakly correlates with a smaller penumbra lesion formation ($r_s=0.22$, $p=0.03$). These correlations are reflected in the chart (Figure 2.2.).

2.5. CT perfusion quantitative measurements

To determine CT perfusion measurements, they were measured in all patients with a confirmed diagnosis of acute cerebral ischemic stroke (n=229) in the hemisphere of the visually identified lesion area. Then additionally, assessing compliance with visully detected area - the core area, if the lesion was detected in all 3 maps - mean transit time (MTT), cerebral blood volume (CBV) and cerebral blood flow (CBF). Penumbra area was determined, if there was a difference between CBF and CBV maps while MTT map showed changes. Measurements were made in all three maps in identified core and penumbra areas with ROI (region of interest) that was adjusted according to the lesion. Gained measurements were compared with findings in contralateral hemisphere normal brain tissue.

CTP maps showed normal finding in 76 out of 229 (33%) cases and pathological findings in 153 (67%) cases. From pathologic cases isolated

irreversible type or **core lesions** were found in 36 (23%) cases (defect area matched in CBV and CBF maps), the isolated reversible type or **penumbra lesion** found in 41 (27%) case (defect area did not match in CBV and CBF maps), a **combined core and penumbra lesion** was found in 76 (50%) cases. Image below shows combined penumbra and core lesion in CT perfusion maps and performed measurements in both hemispheres (Figure 2.3.)

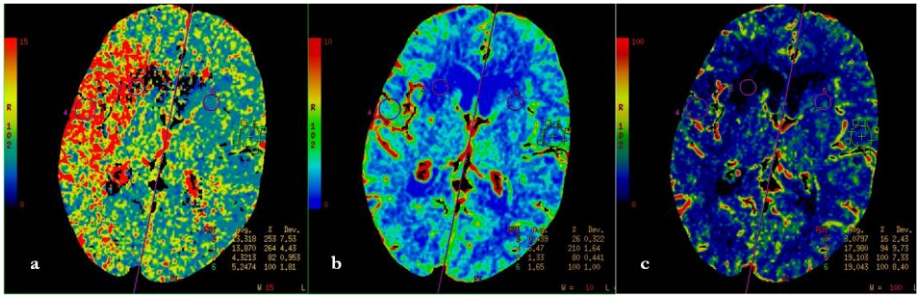

Figure 2.3.Clinical case*.

Female 85 years. Left hemiparesis, 2 hours after onset, a – MTT map, b – CBV map, c – CBF map. All three perfusion maps show irreversible (core) lesion at the level of right caudate nucleus, it is surrounded with penumbra lesion, that is detected by mismatch of CBV and CBF maps and mismatch with MTT map.
* Images form the author's archive.

By data comparison in the area of necrosis, penumbra and normal brain tissue between the mean measured values of MTT, CBV and CBF parameters there were statistically significant differences ($p<0.0001$). MTT measurement values were increased in both - core and penumbra lesion in comparison with normal findings. The CBV values of the penumbra zone were close to normal - slightly below or above it, and with a marked decrease in the area of necrosis. CBF values were decreased in penumbra area and markedly decreased in the core area.

Perfusion parameter relative values, respectively, the percentage of parameter values, were considered to be more reliable, taking into account individual variability of the cerebral hemodynamics parameters and penumbra

and the core area close disposition. Measures were carried out in areas of interest to the opposite hemisphere identical areas, which were defined as 100%. The results are summarized in the table below (Table 2.5).

In comparison of the measurement pairs in core and penumbra zone between mean MTTr relative values no statistically significant difference was seen (p=0.06). Between CBVr and CBFr mean relative values there was a statistically significant difference (p<0.0001).

Table 2.5.

Relative threshold values for perfusion parameters in necrosis and penumbra zone

Lesion type /CTP parameters	**MTTr (%)** Mean transit time	**CBVr (%)** Cerebral blood volume	**CBFr (%)** Cerebral blood flow
Necrosis (n=112)	202.22 (41-324 ±61.61)	39.76 (2-108 ±26.70)	23.81 (1-91 ±16.07)
Median	190	31	22
Mode	150	25	12
Interquartile range	94	34	17
Penumbra (n=117)	215.14 (118-392 ±59.50)	113.09 (18-218±33.74)	62.22 (14-165±22.99)
Median	206	113	60
Moda	230	114	57
Interquartile range	85	45	32
P value (Wilcoxon test)	0.06	<0.0001	<0.0001

The relative values in penumbra zone in 1/2 of the cases ranged from 160 to 240% MTTr with mean value of 196%, CBVr 89-135% with mean value of 112% and CBFr 49-79% with mean value of 60%. From the above we conclude that in order to accurately define the penumbra zone, the threshold values are as follows: MTTr > 160%, and CBVr> 90% and CBFr> 50 %.

To define the type of core lesion relative MTTr values of 150-250%, with mean value of 190%, CBVr 18-52% with mean value of 31% and CBFr 12-30% with mean value of 22%, which results in the following - the core area threshold values are as follows: MTTr > 150%, CBVr <50% CBFr <30%.

Graphical illustrations below reflect the trend of relative parameters in ischemic areas as compared to the opposite hemisphere and determined by the value of 100% for each individual patient (indicated by the dotted line in Fig. 2.4.).

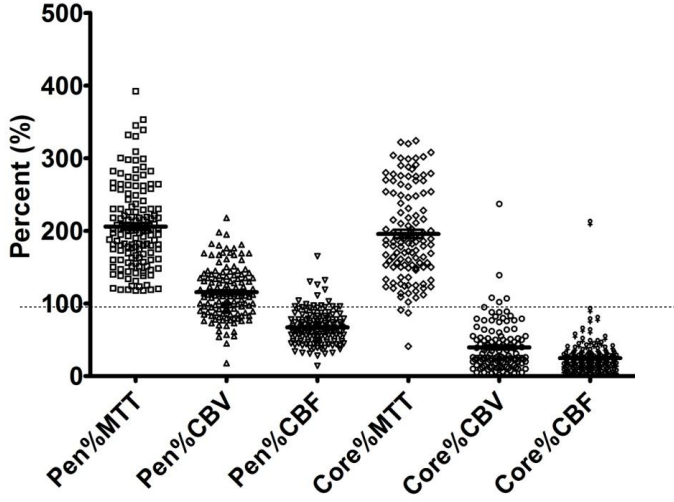

Figure 2.4. Relative CTP parameter value trends in the ischemic areas (core vs. penumbra)

The analyzed results indicate that in cases of increased MTT values it is possible to identify perfusion deficit without definition of the ischemic degree by using a relative threshold value of> 150%. CBF parameter was markedly different and reliable parameter for definition of the defect, so taking into account the variability of CBV values in the penumbra lesion and markedly reduced values in the core lesion, it is possible to differentiate ischemic lesion grades and types (core and penumbra).

Comparing extracranial vascular stenosis group with the CTP parameters by univariate ANOVA test with LSD (Least Significant Difference) post hoc analysis, results showed that the relative MTT values in penumbra zone were higher and CBV and CBF values higher than in severe (70-99%)

stenosis group and lower in occlusion group. This finding indicated that CT perfusion parameters are consistent with more unfavorable haemodynamic status in occlusion group ($p<0.01$).

2.6. Acute cerebral ischemic stroke treatment

Treatment of 229 acute cerebral ischemic stroke patients, in accordance with international and national guidelines, was based on **standard medical treatment** in 153 patients (66.81%) and **active recanalization therapy** - intravenous thrombolysis was carried out in 43 patients (18.8%) or mechanical thrombectomy for 30 patients (13.1%) and 3 (1.3%) patients received combined recanalization therapy - thrombolysis and thrombectomy.

Analysis by types of treatments, **depending on the acute vascular occlusion localization**, showed a statistically significant difference ($p<0.0001$). Although thrombolytic therapy was selected more often in MCA M2 segment occlusion (n=25) and mechanical thrombectomy was selected more often in occlusion of intracranial MCA M1 segment (n=11) and combined extracranial and intracranial occlusion (n=4), no statistically significant difference was found between the atherosclerosis group and the control group ($p>0.05$). Assessing the selected therapy after ischemic location and time, M2 occlusions received thrombolytic therapy within 4.5 hours in most cases, but the M1 and ACI occlusion was rarely treated with thrombolysis, more often was selected for thrombectomy till and after 4.5 hours time window had passed, and the ACI and ACM proximal occlusion over the 4.5 hour time window only by thrombectomy approach.

Neurological and radiological scale score dynamics, at baseline and at discharge or follow-up exams, by therapy type is given in table below (Table 2.6.).

Table 2.6.

Distribution of changes in neurological and radiological scale scores by therapy type

Therapy type	**mRS score** baseline/discharge (median values)	**NIHSS score** baseline/discharge (median values)	**ASPECTS score** baseline/follow-up (median values)
Standard therapy	5/4	8/5	9/8
Intravenous thrombolysis	5/4	13/8	8/8
Mechanic thrombectomy	5/3	15/6	8/7
Thrombolysis and thrombectomy	4/3	10/4	9/7

Although neurological scale scores improve in all therapy types, it should be noted that median baseline NIHSS values in accordance with the clinically more severe CI were more prevalent in the active recanalization treatment group compared with the standard therapy group.

2.7. CT perfusion finding comparison to clinical outcome

For evaluation of diagnostic effectiveness in acute cerebral ischemic stroke (CI) diagnostic radiological parameter ASPECTS at admission and follow up and clinical parameters (NIHSS scale and the mRS scale scores at admission and discharge) were used. We found that baseline ASPECTS is one of the most accurate parameters of the early outcome prediction by the Receiver Operating Characteristics (ROC) curve and logistic regression equation (AUC=0.78; sensitivity 69% and specificity 82%; NPV=0.89 and PPV=0.40. The ASPECTS scores at baseline and at follow-up exams are shown in the ROC curve below (Figure 2.5.).

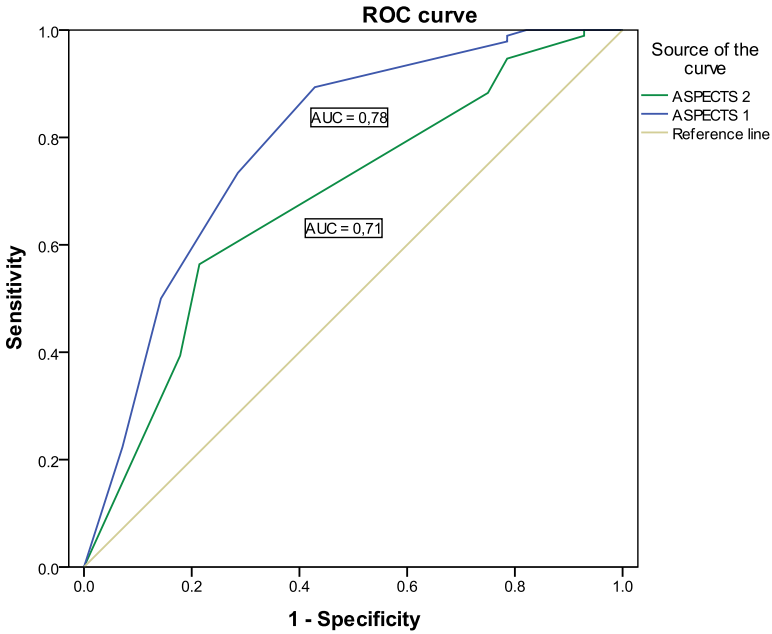

Figure 2.5. Radiological scoring (by ASPECTS scale) accuracy in outcome prediction.

ASPECTS 1 - baseline ASPECTS score; ASPECTS 2 - outcome ASPECTS score

Higher baseline ASPECTS score correlates moderately with lower baseline NIHSS values at admission statistically significant (r_s=0.57; p<0.0001). Also baseline ASPECTS higher values correlate with the lower mRS score at discharge statistically significant (r_s=-4.21, p<0.0001).

Baseline ASPECTS was statistically significant parameter for a favorable outcome (Wald=8.27, p=0.04), as well as collaterals (p=0.017). We used logistic regression analysis to assess possibility of baseline ASPECTS and collaterals to predict the outcome. Based on the ROC curve analysis, it was concluded that this model has a high diagnostic value (AUC=0.78, sensitivity 82% and specificity 64%, NPV=0.93 and PPV=0.38. The odds ratio for a favorable NIHSS outcome (score >16) is 1.3 times higher, if ASPECTS at admission increases per 1 unit, and with good collaterals 3.2 times higher.

Patients with poor or malignant collaterals has 9 times higher odds risk of poor outcome in comparison with patients who have good collaterals (OR=9.05; p<0.0001).

2.8. Multimodal protocol sensitivity, specificity and accuracy in diagnostics of acute cerebral ischemic stroke

To evaluate the multimodal CT protocol sensitivity, specificity and accuracy parameters were evaluated in all cases, that had all 3 examinations (n=306) in comparison with the follow-up data. Characteristics of multimodal protocol methods are shown in table (Table 2.7.).

Table 2.7.

Characteristics of multimodal protocol sensitivity, specificity and accuracy

Type of examination **N=306**	**NCT**	**CTA source images**	**CTA**	**CTP**	**Multimodal protocol**
Sensitivity (%) 95% confidence interval	38 0.30-0.45	48 0.40-0.55	87 0.80-0.91	80 0.75-0.85	79 0.73-0.83
Specificity (%) 95% confidence interval	92 0.85-0.95	93 0.86-0.96	72 0.63-0.79	89 0.78-0.95	84 0.71-0.91
Accuracy (%) 95% confidence interval	62 0.55-0.67	68 0.65-0.75	80 0.77-0.83	84 0.80-0.92	85 0.83-0.90
Positive predictive value (PPV) 95% confidence interval	0.85 0.74-0.92	0.89 0.80-0.94	0.79 0.72-0.84	0.94 0.89-0.97	0.80 0.74-0.85
Negative predictive value (NPV) 95% confidence interval	0.54 0.47-0.60	0.58 0.51-0.65	0.81 0.73-0.87	0.74 0.66-0.81	0.70 0.66-0.76
Area under curve (AUC) 95% confidence interval	0.651 0.57-0.72	0.729 0.66-0.79	0.766 0.68-0.84	0.88 0.84-0.90	0.81 0.73-0.88

2.9. CT perfusion interpretation consistency

For assessing the consistency of CT perfusion methods an inter-rater reliability comparison was carried out between two interpreters radiologists in 195 cases. Cohen's kappa analysis showed that the interpretation consistency degree is assessed as moderate and statistically significant (kappa=0.7; $p<0.001$). Comparing the intra-rater reliability – retrospective evaluation of 34 cases was done. There was a difference in interpretation only in 2 cases. One evaluator's consistency of interpretation is considered as good and statistically significant (kappa=0.8; $p<0.001$).

3. DISCUSSION

Functional radiological examinations such as CT perfusion scans (CTP) in addition to the standard diagnostic test – non enhanced computed tomography of the brain are becoming more and more essential in the modern diagnostics of acute cerebral ischemic stroke. It is readily available, timely, minimaly invasive and provides clinically relevant data on brain tissue vascularity, perfusion and function at early stages of the stroke [Leiva-Salinas et al., 2011].

There are authors who believe that tissue viability assessment by CT perfusion in acute cerebral ischemic stroke patients is associated with a number of problems, not just the visual interpretation, but there is little credibility in perfusion measurements [Fiorella et al., 2004] and conflicting cerebral blood volume and flow parameters [Wintermark et al., 2008], as well as lack of standardized imaging protocols, and post-processing [Kamalian et al., 2011]. Accurate irreversible ischemic tissue differentiation from potentially reversible tissue by quantitative measurement is essential, because acute cerebral ischemic stroke treatment strategy currently is based on early and effective recanalization therapy for patients for whom it could provide potential to a positive outcome [Broderick et al., 2013].

A factor that affects the other perfusion parameters is the degree of reperfusion, which correlates directly with collateral efficiency. Collateral profile characteristics defined in CT angiography may influence therapy strategy by identifying the patients who are at high pre-treatment risk of a large infarct volume, so-called malignant infarctions and they most likely would not improve during revascularization therapy [Puetz et al., 2010].

Variable acute cerebral ischemic stroke outcomes depend not only on timely diagnosis, patient management and adequate treatment, but also on the individual hemodynamics compensatory mechanisms that are affected by a number of additional factors - changes in atherosclerotic neck and head blood vessels, vascular occlusion, location and collateral blood flow - all of these

elements together give basis for further patient prognosis [Romero et al., 2009, Souza et al., 2012].

This study primarily analyzed the following aspects of acute cerebral ischemic stroke diagnosis: standardized CT perfusion parameter threshold values for detection of reversible and irreversible ischemic lesion, blood vessel changes - including atherosclerosis and collateral blood supply effects on brain perfusion and CT multimodal methodology role in common acute cerebral ischemic stroke diagnostic and treatment strategy algorithm by studying early radiological parameters.

3.1. Stenotic changes in extracranial and intracranial blood vessels

For detailed analysis of anterior circulation stroke cases (n=189) a subdivision by stenotic grade of extracranial blood vessels on CT angiography was used, according to international classification by NASCET [Allan et al., 1993]. There was a tendency of cardioembolic and small vessel etiology stroke subtypes in mild stenosis (<49%), while the occlusion group had more atherosclerotic etiology subtype. Control group without athersoclerosis had tendency to cardioembolic as well as unspecified cause and other cause stroke subtypes. There was tendency of athersoclerotic changes in age group above 50 years of age without statistical significance between female and male.

Most common site of intracranial stenotic changes 70-99% was seen at middle cerebral artery M2 segment. Recently was published study, where authors stated that small vessel atherosclerosis caused stroke had better outcome clinically and radiologically with less necrosis growth in comparison to other stroke etiology subtypes, [Kim et al., 2011], though our study had too few patients with such subtype to draw a conclusion. For better evaluation of atherosclerosis related changes in extracranial and intracranial blood vessels further we analyzed occlusion location.

Extracranial and intracranial blood vessel alteration discussion is integrated in further chapters as well.

3.2. Acute vessel occlusion location

We divided vessel occlusion sites in subtypes: intracranial proximal median cerebral artery (MCA) occlusion at M1 segment, distal at M2 segment, proximal internal carotid artery (ICA) occlusion or total ICA and MCA proximal occlusion [Qureshi et al., 2004].

In general of all intracranial occlusion location most common site was MCA M2 segment, that was more frequently seen in patient group with mild (> 49%) and moderate (50-69%) extracranial stenosis and was related to cardioembolic CI subtype and to a lesser extent to atherothrombotic CI subtype ($p<0.0001$). There was no difference in intracranial vessel stenosis and occlusion location between study and control groups ($p>0.05$).

Intracranial occlusion location correlates to perfusion CT core defect size or ASPECTS score at admission ($p<0.0001$) and follow-up examinations ($p<0.0001$). ASPECTS score threshold value 7 was used for radiological differentiation between potentially favourable and unfavourable outcome (≥7 favourable; <7 unfavourable), similarly to other authors – Dzialowski and group found that ASPECTS score has a prognostic value to evaluate outcome independently from thrombolysis therapy use [Dzialowski et al., 2006]. There are statements in other publications that ASPECTS score use in perfusion CT setting is even more precise parameter in predicting outcome than in non-enhanced CT images [Lee et al., 2013, Sillanpaa et al., 2011].

In our study ASPECTS score showed lower mean values in cases of isolated MCA M1 segment and ICA proximal occlusion as well as in cases of combined ICA and MCA occlusion - 6 to 7 points, indicating association with an unfavorable outcome ($p<0.0001$). Whereas in patients of no evident intracranial occlusion ASPECTS score was above 9 and in cases of MCA M2 segment occlusion - above 8, that correlated to favorable outcome and was statistically significant ($p<0.0001$).

We revealed statistically significant correlation between occlusion site and NIHSS and mRS scores at discharge ($p<0,05$).

3.3. Collaterals

Assessing the distribution of collaterals using the CTA method in acute cerebral ischemic stroke (CI) patients in this study there were defined three sub-types - malignant, poor and good. The system of evaluation of collaterals in our case was adapted from Tan and authors [Tan et al., 2007] where the degrees were based on the reduced collateralization within more or less than 50% of the occlusion territory, and there we added a special subtype – malignant collaterals similar to a recent study [Souza et al., 2012]. Souza and the co-authors in their study analyzed the CTA of collaterals and the clinical outcome after 3 months using the mRS scale. Assessing the patients according to the type of treatment, the collateral score predicted dichotomized functional outcome and the final infarct size only for untreated patients [Souza et al., 2012]. This finding was controversial among authors of different publications. Angermaier and co-authors demonstrated that the CTA collateral grade was an independent predictor of the final infarct volume in stroke patients treated with endovascular therapy [Angermaier et al., 2011]. But other authors stated that there is higher recanalization rate with good collaterals [Bang et al., 2011]. On the other hand, Rosenthal and the group reported that CTA collaterals had a positive impact on the outcome of patients who did not achieve complete recanalization, and no impact in patients who were completely recanalized at DSA [Rosenthal et al., 2008].

Recent literature proposes a number of hypotheses regarding the development mechanisms of intracranial collaterals and their role in clinical outcome of acute cerebral ischemia. The **first hypothesis** states that a long-term haemodynamic insufficiency observed in intracranial atherosclerosis contributes to development of intracranial collaterals and the tissue adapt to subsequent ischemia and concluded that collaterals have a protective effect on the brain tissue in severe intracranial stenoses [Liebeskind et al., 2011]. In our study patients with intracranial stenoses till 99% had only good collaterals, although considering the small number of patients (n=21) the interpretation of this finding might be ambiguous. Lau and co-authors in their study stated that

antegrade flow or reperfusion affects blood flow in the distal segments, and, in situations of impaired antegrade blood supply collaterals are the ones which provide cerebral blood flow compensation and stabilization within the ischemic area. In cases of complete occlusion collaterals are not able to provide a good long-term stabilization of the blood flow, and therefore it is recommended that this parameter is used as a prognostic marker in severe intracranial stenosis [Lau et al., 2012]. This is complemented by the conclusion from Kaplan and the co-authors that weakened brain reperfusion and insufficient collateral blood supply reinforces the impact of embolism because microemboli are not washed-out within areas of hypoperfusion, and this contributes to the development of ischemia [Caplan et al., 1998].

The second hypothesis says that in patients with acute ischemic stroke due to occlusion of the proximal artery, collaterals in CT angiography correlates with the initial core size. Very poor collaterals are highly specific indicator of the large volume lesions and predicts poor functional outcome [Souza et al., 2012; Lima et al., 2010]. In our study we found a statistically significant correlation between the occlusion site and type of collaterals ($p<0.0001$), and concluded that in cases of wider or more proximally located occlusion segment less collaterals were seen. In patients with occlusion of more peripheral type - MCA M2 segment good collaterals were found in most cases and the largest proportion of malignant collaterals accounted for cases of proximal ICA occlusions (30%).

Assessing the type of collaterals and CT perfusion defect types (isolated penumbra, core or a combination of lesions) we found that the isolated penumbra zone was observed in patients with good collaterals in most cases (90%), less often in patients with poor collaterals (10%) and these patients did not have malignant collaterals. In case of a combined damage (both core and penumbra) a proportion of less malignant collaterals (10%) was found and more pronounced proportion of good collaterals (61%) was present while in cases of normal CT perfusion findings only good collaterals were found.

The third hypothesis claims that the collateral blood vessels develop at embryonic stage, together with the central nervous system and their number

in a small volume changes after birth [Romero et al., 2009]. The protective action of collaterals thus depends on a number of factors: anatomic variations, arterial blood pressure, age as well as duration of occlusion.

Experimental studies in animals showed that the first alterations of leptomeningeal collateral flow can be observed already 1-4 seconds following the occlusion, indicating that metabolic factors have less impact [Symon et al., 1963]. With continuing of long-term ICA occlusion, a dilatation of the posterior circulation arteries for 40% proximally was observed after 1 week, and about 72% - after three weeks [Meyer et al., 1957]. However, the actual process of angiogenesis in the human brain still has not been fully explored [Romero et al., 2009].

We found that both poor and good collaterals were found in all extracranial stenoses groups, and we did not yield a statistically significant difference in distribution of collateral types between extracranial atherosclerosis and control groups ($p>0.05$); we concluded that solely extracranial atherosclerosis (stenosis) had no significant impact on the collateral status in our study.

The time before the examination in our study did not affect the status of the collaterals, and it coincides with publications from other authors [Christoforidis et al., 2005]. As proved by experimental studies in animals, genetic variability is a major determinant factor for development of collaterals [Zhang et al., 2010]. Based on the latter hypothesis the collateral status in case of progressive ischemia should not deteriorate. A number of authors state that the collateral status is a robust and independent determinant of the clinical outcome, good collateral flow is a factor for favorable clinical outcome and its deficit is considered to be an adverse factor [Tan et al., 2007; Maas et al., 2009].

Although in generally it is conceptually clear that in untreated patients (with lower chance of recanalization) the proportion of collaterals share a role in the final clinical outcome and the degree of tissue damage, it is however not to say that all patients with good collaterals are expected to yield good treatment result, as patients should not be selected for the recanalization

treatment based solely on the proportion of collaterals. Evaluation of brain collaterals along with cerebral perfusion and clinical indicators in CI patients provides a wider insight into the assessment of cerebrovascular conditions. Further studies on the effect of these factors on the choice of treatment tactics can improve the understanding of the role of functional tests in patients with acute cerebral ischemic stroke in both acute and chronic extracranial vascular changes, and this would require a prospective study involving a larger cohort group.

3.4. Perfusion lesion type, garde, location and size

Perfusion defect on perfusion CT maps were defined by lesion **types isolated or combined** and we found isolated core (15%), isolated penumbra (22%) and combined penumbra and core lesion (40%)**. By grade** there were irreversible or core and reversible or penumbra lesion. Given perfusion lesion types did not show statistically significant difference between study group with atherosclerosis and control group, as well as there were no differences among age groups or gender ($p>0.05$).

Core type lesion by location was more frequently seen as partial hemisphere lesion or as a total hemisphere defect ($p<0.0001$). Combined lesion (penumbra and core) cases had necrosis at basal ganglia and hemispheres at the same time and penumbra zone was only in periphery of hemisphere ($p<0.0001$), but this penumbra zone frequently transformed into necrosis in both areas – basal ganglia and hemisphere at follow-up imaging.

For analysis of lesion size we used radiological ASPECTS score our study indicated that good collaterals correlate with lesser necrosis size ($p<0.0001$), while in patients without atherosclerosis and poor collaterals more extensive necrotic lesion prevailed ($p=0.01$). Similar findings were assessed also by other authors comparing the presence of collateral blood flow and extent of the MR perfusion lesion, concluding that good collateral flow is associated with larger penumbra and smaller ischemic core lesion at baseline [Bang, 2011, Miteff, 2009], and it extends the viability of penumbra in maintained reperfusion, thus extending the time window for treatment. Good

collaterals restrict extension of ischemic core and define the final ischemic lesion volume [Menon, 2013], that corresponds to our study data.

3.5. Quantitative measurements and threshold values of CT perfusion

As in former CT perfusion studies by other authors [Ledezma et al., 2009; Wintermark et al., 2002, 2006], also in this study we defined the grades of ischemic lesion: a potentially reversible lesion or penumbra zone as a mismatch between cerebral blood volume/flow parameters (CBV/CBF) as well as necrosis or core zone as appropriate match of cerebral blood volume/flow changes with extended mean transit time (the time between the arterial inflow and venous drainage within the examined area).

The absolute values influenced by an individual proportion between the gray and the white matters [Konstas et al., 2010; Schaefer et al., 2006]. To obtain an individually accurate interpretation of findings in quantitative perfusion measurements, in this study the absolute values are considered to be less reliable because the parameters for gray and white brain matter described in literature are different [Wintermark et al., 2002; Wintermark et al., 2006, Feyen et al., 2011] and in case of ischemia often are assessed as a common area. Use of normal values for a certain type of brain matter does not neccessarily provide a correct impression on the severity of the lesion. Also considering the individual variability of cerebral hemodynamics parameters as well as the close disposition of penumbra and core areas the relative values obtained by comparison with normal brain tissue of the contralateral hemisphere (MTTr, CBVr and CBFr) were considered more reliable. Respectively, measurements were performed in zones of target lesions comparing with identical areas in the contralateral hemisphere that was set as 100%.

In order to accurately define the areas of potentially reversible tissue along with the irreversible tissue lesion within the ischemic area in this study there were obtained the following statistically significant perfusion parameter threshold values: 1) for the penumbra area MTTr >150%, while the average

reduction in CBFr was >50% and CBVr was almost normal or increased, i.e., 90-110% 2) for the core zone MTTr was increased, i.e., >150%, CBVr was significantly reduced, i.e., <50% and CBFr was <30%. A new borderline area in this study was observed with measured data: an average reduction of CBVr, i.e., 50-90% and an average reduction of CBFr, i.e., 30-50%, which was considered to be the penumbra area, but closer to the lowest values was called as deep penumbra, and it reflected the degree of depletion of autoregulation mechanisms.

This type of data with distinct parameter threshold values were also published by a group of co-authors under guidance of Srinivasan [Srinivasan et al., 2006], which yielded similar threshold values not specifying MTTr values and for the definition of core used lower CBVr values (<40%) than in this study (<50%). Certain authors point out that the relative mean transit time describes the best ischemic penumbra zone during the first hours following the onset [Leiva-Salinas, 2011] and in the mentioned study, the authors stated that MTTr limit of >145% (increased transit time by at least 145% compared to the intact contralateral hemisphere) is optimal. Our results with CBFr in the case of core <30% correlate to other published data of other authors which confirmed that ischemic tissue with CBF >35% could be rescued if the re-canalization is performed within 5 hours from the onset of symptoms [Schaefer et al., 2006].

However, the consensus on the optimal CT perfusion values still has not been reached [Dani et al., 2012].

In our study there were cases with increased mean transit time within a large area of hemisphere without corresponding changes in cerebral blood volume and flow maps, and in these patients the relative MTTr values did not exceed the threshold value of 150% - this finding was considered as oligaemia or false-positive penumbra.

Threshold values have a role in cases of ambiguous visual findings as an indicator of lesion grade. Due to slower collateral blood supply or hemodynamically significant stenosis in intracranial or extracranial blood vessels can increase the mean transit time in distinct artery circulation area of also not being related to stroke [Souza et al., 2012]. Such findings should be

assessed critically and should not be interpreted as ischemia. In such cases, stroke-like conditions should be considered, such as transient ischemic attack, subdural hematoma, neoplasm, vasospasm, venous thrombosis, or even seizures induced by hypoperfusion [Gelfand et al, 2010; Best et al., 2012]. This phenomenon points out that the interpretation of CT perfusion exam should always be combined with the evaluation of CT angiography images to rule out a critical stenosis or occlusion in extracranial blood vessels. Attention must also be focused to the clinical complaints which do not match radiological findings.

The other large group, where it is essential to use threshold values, are patients with previous cerebral infarction, in such patients clinical signs of decompensation are frequently observed, which should be differentiated from recurrent stroke within a the same circulation territory. Consequently, we conclude that simultaneous application of both CT angiography and CT perfusion used in this study enables reliable differentiation between acute cerebral ischemia and similar conditions.

Assessing the CT perfusion parameters we found that the relative values in both penumbra and core areas were with increase of MTTr and higher CBVr as well as CBFr values in the group of severe stenoses (70-99%) at extracranial blood vessels and at lower values in the group of internal carotid artery occlusion. Our findings suggest that the CT perfusion parameters in the occlusion group are in comparably worse haemodynamic status. Patients with moderate extracranial stenosis with visually assessed necrosis have better hemodynamics than other groups of patients ($p< 0.01$).

Our study results suggest that using increased MTTr parameter we could confirm perfusion deficit with no certainty about the grade of ischemic defect. The CBFr parameter was markedly different and statistically significant in specifying the defect type ($p <0.0001$), thus taking into account the variability of CBVr values in case of penumbra lesion and markedly reduced values in core lesion. It is possible to differentiate types and grades of ischemic lesion (core and penumbra). Statistically confident data that showed difference in perfusion values between patients with and without atherosclerosis in this study were not obtained.

3.6. CT perfusion finding correlation to clinical status and outcome in patients with cerebral ischemic stroke

In order to assess the consistency of radiological findings with clinical situations of acute cerebral ischemia in this study the visual score of the radiological lesion score (ASPECTS) was applied on perfusion CT (CTP) images, and its findings were compared to the values from scores of neurological status and functional disability (NIHSS and mRS).

To evaluate the correlation between the radiological findings and the outcome, the NIHSS score at discharge groups were defined as follows: favorable outcome (<16 points) and unfavorable outcome (≥ 16 points), as specified classification in other studies [Brott et al., 1989; Adams et al., 1993]. We found that higher CTP ASPECTS score values correlate with lower values of NIHSS and mRS scores at discharge ($p< 0.0001$).

There was an unequivocal favorable outcome in small vessel etiology CI subtype in comparison to other subtypes ($p=0.002$), that had both – favorable and unfavorable outcome with tendency to favorable outcome, mentioned correlates to recently published data, where intracranial atherosclerotic stroke showed favorable clinical (OR=3.45) and radiological outcomes (OR=10.4) compared with other subtypes [Kim et al., 2011].

In the evaluation of diagnostic performance efficiency aspects in assessment of acute cerebral ischemic stroke (CI) by the ASPECTS score, from our results it can be concluded that this was one of the most accurate parameters in early prognosis of outcome with a sensitivity of 69 % and specificity of 82%.

The application of the ASPECTS score in the perfusion examination provides the ability to early determine the size of the cerebral stroke within the perfusion territory of middle cerebral artery. Aviv and the co-authors studied non-contrast CT and CT perfusion examinations of 36 patients within 3 hours after onset of the symptoms and the ASPECTS values were blindly interpreted by three experienced radiologists. A positive response to the treatment was concerned if within 24 hours the result according to NIHSS was equal to 8 or

less. The follow-up CT examination and 3-month mRS were chosen to be the radiological and clinical criteria. The CT perfusion CBV and non-contrast CT examination ASPECTS values were of similar radiological correlation (0.6 and 0.5) and were the best predictors of stroke volume and correlated to irreversible neurological deficits [Aviv et al. 2007]. Also in our study good clinical outcome was not achieved in patients with the ASPECTS value below 7 points. Similar findings were published by Abel and the co-authors [Abels et al., 2012].

Menon and co-authors using analysis with multiple dependent variables found that the 3 most important imaging factors determining the clinical outcome along with age were: collateral status, core volume as well as clot-caused vascular occlusion. According to our study the age did not affect the status of the collaterals, but in the logistic regression model a significant impact of the collateral status on the outcome along with the core damage volume was detected (sensitivity 69%, specificity 82%, NPV=0.89, PPV=0.40). We did not obtain evidence that the initial NIHSS scale score predicted the clinical outcome ($p>0.05$), as it was stated in other studies as well [Maas et al., 2009, Menon et al., 2010]. Our results confirmed - if the ASPECTS value at admission was greater than 1 unit then the chance for a good outcome was higher (OR=1.3); moreover, if the finding was combined with good collaterals, the chances for a favorable outcome were even more pronounced (OR=3.2). Patients with poor and malignant collaterals have a greater risk for a poor outcome (OR=9) when compared with patients who have good collaterals. The created logistic regression model explained 30% of the total changes, and in general the outcome was predictable in 80% of patients. Collaterals were a statistically significant parameter for prediction of favorable outcome ($p=0.017$) as well as the ASPECTS value at admission ($p=0.04$).

In a meta-analysis of 2013 regarding CT perfusion it was emphasized that the extent of penumbra and core lesion at the admission is an important criterion for the prediction of outcome, possibly exceeding the estimated value of the admission NIHSS score [Jauch et al., 2013].

3.7. Treatment

If an acute cerebral ischemic stroke is detected early and viable brain tissue zone is found by using multimodal CT methods, it makes possible in cases eligible for selective differentiated treatment to realize an active etiopathogenetic therapy, i.e., intravenous thrombolysis up to 4.5 hours or 270 minutes after the onset of symptoms, or an intraarterial thrombolysis, or mechanical thrombectomy till up to 6 hours, or 360 minutes after symptom onset according to the guidelines. The earlier the active treatment is initiated, the more likely the outcome is favorable [Jauch et al., 2013]. With every minute closer to the time limit the patient's compensatory autoregulation mechanisms are depleting therefore commonly, in spite of an early hospitalization, the patient's clinical condition and radiological findings preclude thrombolysis. Both interventional radiology techniques and thrombolysis have a high risk of bleeding complications, so careful patient selection is very important [del Zoppo et al. 2009]

In this study, the treatment of an acute cerebral ischemic stroke (CI) was based on standard medical treatment in 66.8% of the CI cases, while in a smaller number of cases an active recanalization therapy - intravenous thrombolysis in 18.8%, mechanical thrombectomy in 13.1% and combined recanalization therapy - both thrombolysis and thrombectomy was performed in 1.3% (130 minutes). In cases of wake up strokes and patients with unknown exact onset time of symptoms perfusion defect zone and intracranial vessel occlusion was seen more frequently, this being indicative of need for vascular and perfusion imaging for these patients, to assist therapeutic decision making [Silva et al., 2010]. In the study, published by Vendrell and co-authors regarding comparison between intravenous thrombolysis and thrombectomy in 123 patients, it was reported that 3-month neurological status (mRS score $\leq$2) in case of an occlusion of the proximal part of the middle cerebral artery has been with improvement in thrombectomy patients (50% for thrombolysis and 77 % for thrombectomy), and no haemorrhage was detected. This showed that thrombectomy is to be considered as an alternative method following failure of

intravenous thrombolysis within a specified time period from the symptom onset. It is known that in the event of the proximal internal carotid artery (ICA) and middle cerebral artery (MCA) occlusion the degree of recanalization during thrombolysis is low which contributes to poor clinical outcome [Vendrell et al. 2013]. In our study a similar strategy was applied. Assessing the selected treatment by the occlusion location and time, in most of M2 occlusion cases the patients received thrombolytic therapy within 4.5 hours, but patients of isolated ACM M1 or proximal ICA occlusion rarely were treated solely by thrombolysis; in these situations more often the method of choice was thrombectomy within 4.5 hours as well as after this time, and combined occlusions of ACI and ACM beyond the 4.5 hour time window were treated solely by thrombectomy.

In 2013 randomized studies were published (IMS III, 2013, SYNTHESIS Expansion 2013) [Ciccone et al., 2013, Broderick et al., 2013] regarding comparison between intravenous thrombolysis and various endovascular approaches. Results from these studies suggest that mechanical thrombectomy cannot be considered to be superior, and both methods are equally safe but according to the guidelines thrombectomy is considered as a treatment method in selected cases while the intravenous thrombolysis is considered to be the main recanalizing treatment method, and further studies are needed for evaluation of indications for mechanical thrombectomy as well as for comparison of efficacy with other treatment methods in case of the cerebral infarction [Jauch et al., 2013; Wintermark et al., 2013].

Variable outcomes of an acute cerebral ischemic stroke depend not only on the timely diagnosis, the patient's progress and choice of an appropriate treatment, but also on individual hemodynamics compensatory mechanisms that are affected by a number of additional factors (other diseases, extent of atherosclerotic changes, collaterals, etc.) - all those elements together represent the future prognosis for a patient and give rise to opportunities for further research [Romero et al., 2009; Souza et al., 2012].

3.8. Multimodal computed tomography imaging protocol

In this study, a multimodal CT protocol was used for prospective analysis of all 3 examinations integrated, applying a standardized protocol with retrospective comparison with follow-up examination or clinical data. The importance of proper methodology for the perfusion CT imaging can hardly be overestimated; the slices of examination should contain both reference blood vessels and the ischemic lesion, and patient movements that may cause artefacts and affect the final results should be prevented [del Lucas et al., 2008].

There are diverse opinions on the sequence of CT modalities in the literature [Leiva-Salinas et al., 2011]. In this study, CTA was always performed before CTP because it helped to choose the area of the limited coverage for further CTP assessment and to determine time for the maximum enhancement from the administration of contrast media that played significant role in further interpretation.

CT angiography was essential in this study to assess the location and the extent of occlusion of the blood vessel and to detect collateral blood supply, atherosclerotic changes in the blood vessels of the neck and head. The full path of brachiocephalic blood vessels was included in the scanned area and it was particularly important in planning of further invasive treatment of the patients before mechanical thrombectomy as it gave an overview of the individual anatomical variations and other pathology. In this study, the CTA method combined with postprocessing programs for blood vessels showed 87% sensitivity, 72% specificity and 80% accuracy which correlate with data of other authors, 65-100%, 63-100% and 64-100%, respectively [Hirai et al., 2002; Randoux et al., 2001].

The time of multimodal CT examination in our study was short (on average 10 minutes). One should, however, take into account that proper postprocessing and interpretation of images require more time than NCT, and it is important that examinations do not delay the initiation of recanalization therapy [Jauch et al., 2013].

In recently published studies, authors claim that core and penumbra lesions detected in perfusion CT provide independent information which cannot be predicted only by the data of NCT or CTA examination and are important as criteria for the clinical outcome [Garcia-Bermejo et al., 2013]. In our study, the precision of NCT examination and basic CTA images was assessed as weak (35-48% sensitivity, 92-93% specificity); however, CTP examination showed good efficiency (80% sensitivity, 89% specificity). In a recently published meta-analysis, the pooled data from 15 perfusion CT studies involving 1,107 patients were compared, the total analysis of the CTP method revealed 80-85% sensitivity and 90-97% specificity [Biesbroek et al., 2013] which corresponds to the data of our study. Several false positive cases included patients with TIA, chronic internal carotid artery subocclusion and occlusion. The majority of false negative cases were lacunar CIs, because they were not included in the scanning area.

In this study, the total efficacy of a multimodal protocol in early diagnostics of CI was assessed as good.

In our view, the main advantages of a multimodal protocol in the diagnostics of acute cerebral ischemic stroke are as follows: availability for 24 hours a day, short examination time, precise imaging of the path and alteration of extracranial and intracranial blood vessels, imaging of the cerebral collateral blood supply, precision of quantitative perfusion, application of absolute and relative parameters and possibility to detect other intracranial pathologies. Further CT follow-up provides an opportunity to assess the results of treatment.

In current actual guidelines for stroke management [Jauch et al., 2013], the recommendation to use a perfusion method in case of an acute cerebral ischemic stroke is still optional as the standardization and validation of the perfusion CT methodology is required as well as additional studies on imaging-based treatment decision impact on the outcome.

3.9. Perfusion CT interpretation agreement

In order to assess the consistency of perfusion CT interpretation the comparison of the result agreement between two interpreters (radiologists) was performed. We concluded that the degree of agreement could be rated as medium (kappa=0.7) and was comparable with the previously published data from Scharf et al. (kappa=0.65) [Scharf et al., 2006]. The result is most likely is attributed to the different levels of experience and competency of the radiologists in the interpretation of the relevant studies. Whereas, the degree of agreement can be assessed as good (kappa coefficient is 0.8) when repeated assessments of one interpreter are compared. The relative high interpretation agreement between two raters in our study is admittedly associated with the use of an automated postprocessing protocol of perfusion CT images. Similar studies on the variability of data of perfusion CT have already been performed [Fiorella et al., 2004]. In these studies, the authors analyzed the interpretations of isolated perfusion maps in the manual mode and found notably greater variability of the results (CBV=0.69; CBF=0.70 and MTT=0.86) which can be partly attributed to the variable and operator-dependant coding of the color scale of perfusion CT maps. Each manufacturer of the

The results of our study enable one to conclude that the variability of interpretation may be explained by diversity of the clinical situation of an acute ischemic stroke with a high degree of reliability if the study is assessed by a competent radiologist in the interpretation of multimodal CT protocol modalities.

The first hypothesis of this study - that necrosis and penumbra extent in acute ischemic stroke is different in patients with or without atherosclerotic changes in brachiocephalic blood vessels and necrosis extent correlates to stenosis grade and occlusion location - was validated partly, because ischemic lesion extent in our study was mainly determined by vessel occlusion and collateral blood supply and direct extracranial stenosis grade did not correlate to lesion size. The second hypothesis - that marked functional collateral

network is seen in patients with chronic intracranial circulation impairment due to atherosclerotic changes in brachiocefalic vessels, and increased reperfusion through existing collaterals correlates to favorable outcome - was not validated in its first part, because good collaterals were seen independently from atherosclerotic changes in this study, but implicitly was validated in second part, because good collaterals solely and in combination with small baseline necrosis lesion are reliable favorable outcome markers.

4. CONCLUSIONS

1. Using standardized multimodal CT examination protocols for acute cerebral ischemic stroke patients one can reliably obtain important early information about pathophysiology and morphology of a potentially reversible or irreversible ischemic lesion of brain tissue, and simultaneously determine precisely the neck and head vessel alterations as well as collateral blood vessel status, that has significant role in further treatment strategy.

2. Chronic atherosclerotic changes and stenoses cause brain perfusion impairment. These alterations correlate positively with findings on CT perfusion images. Extracranial blood vessel stenosis >50% show hemodynamically better perfusion parameters in comparison to occlusion. Intracranial blood vessel occlusion correlates with the extent of necrosis.

3. Brain perfusion parameters and ischemic lesion size are mainly associated with extracranial and/or intracranial blood vessel occlusion location as well as collateral blood supply status.

4. Baseline of good collaterals and a small size ischemic lesion are statistically reliable parameters for a favorable clinical outcome and reliably correlate with neurological (NIHSS) and functional deficit (mRS) score values, but they are not directly associated with atherosclerotic changes in brachiocephalic blood vessels. Perfusion defect extent defined by ASPECTS scale score ≥ 7 can be used as potential criterion for favorable outcome.

5. In addition to the main cerebral perfusion deficit characteristics - cerebral blood volume / flow mismatch with increased mean transit time, there is an additional role for relative threshold values (comparison to contralateral side) in definition of ischemic lesion.

6. The following relative threshold values can be used for accurate definition of irreversible and potentially reversible lesion: increased MTT>150%, penumbra zone characterized as moderate decrease of CBFr>50% and almost normal or increased CBVr 90-110%; core zone characterized as marked decrease of CBV<50% and CBFr<30%. Threshold values play a role in presence of ambiguous visual findings as well as in cases of false positive penumbra and recurrent ischemic strokes.

5. RECOMMENDATIONS

1. Multimodal computed tomography (CT) diagnostics using standardized protocol is recommended with sequence of examination methods as follows - non-enhanced brain CT, CT angiography and CT perfusion. This will allow to interpret simultaneously brain parenchyma, course of blood vessels and their alterations, presence of collateral blood flow and to evaluate cerebral perfusion. Multimodal CT examination yields clinically relevant additional information fast and this may be valuable in early choice of treatment for acute ischemic stroke patients.
2. Application of semi-automated and automated post-processing CT perfusion protocols allows standardizing image interpretation and is recommended for daily practice in order to reduce the variability of result interpretation as well as to increase the diagnostic value of the method.
3. CT perfusion threshold values in context of visual findings for assessment of potentially reversible (penumbra) and irreversible (core) ischemic injury can be used in daily practice to improve the differentiation of an ischemic lesion.
4. If the patient's clinical symptoms are not consistent with the perfusion CT penumbra findings, careful review of all available images should be performed to identify possible situations which may lead to false positive penumbra findings. Recognizing of such situations enables clarifying of the diagnosis and reduces the risk to perform an unnecessary thrombolytic treatment
5. Considering the potential of the CT perfusion for reliable differentiation of ischemic penumbra and core damage along with an early assessment of their extent and localization, in the context of published evidence on relationship of the findings with the potential clinical outcome, it is advisable to include this imaging method in the algorithm of diagnosis of patients with early acute cerebral ischemic stroke of up to 6 hours from the onset of symptoms, as well as in patients with unknown exact onset time of symptoms.

6. PUBLICATIONS AND PRESENTATIONS ON RESEARCH THEME

Publications (scientific articles) on research theme:

1. **Radzina M.,** Krumina G., Kupcs K., Miglane E. Perfusion computed tomography relative threshold values in definition of acute cerebral ischemic stroke lesions. Acta Radiologica Short Reports 2013;2:6. doi: 10.1177/ 2047981613486099.
2. **Radzina M.**, Krumina G., Kupcs K., Miglane E. Computed tomography perfusion measurements for definition of lesions in early acute stroke. Open Journal of Clinical Diagnostics, 3, 9-13. doi: 10.4236/ojcd. 2013.31003.
3. **Radziņa M.,** Krūmiņa G., Kupčs K., Miglāne E. Datortomogrāfijas perfūzijas relatīvās robežvērtības agrīna akūta insulta diagnostikā. Rīgas Stradiņa universitātes zinātnisko rakstu krājums, 2011, 2.sēj.:182-189.
4. Priede Z., Ķēniņa V., Miglāne E., Millers A., Pūcīte E., **Radziņa M.** S-100 proteīns kā cerebrāla infarkta plašuma un iznākuma prognostisks marķieris. Rīgas Stradiņa universitāte, Zinātniskie raksti, 1.sēj.: 86-90.
5. **Radziņa M.,** Krūmiņa G., Kupčs K., Miglāne E., Dzelzīte S., Millers A., Priede Z. Multimodāla datortomogrāfiska izmeklēšana agrīna akūta insulta diagnostikā un terapijas taktikas plānošanā. Rīgas Stradiņa universitāte, Zinātniskie raksti, 1. sēj.: 397-405.
6. **Radziņa M.,** Krūmiņa G., Pūpols J. Daudzslāņu spirāles CT angiogrāfijas iespējas intrakraniālo un ekstrakraniālo artēriju disekciju diagnostikā. Rīgas Stradiņa universitāte, Zinātniskie raksti. 1. sēj.: 224-229.

Published abstracts on research theme:

1. **Radzina M**, Krumina G, Kupcs K, Miglane E. CT brain perfusion patterns in acute stroke with atherosclerosis of extracranial blood vessels. Neuroradiology 2012, Vol. 54, Suppl. 1, p. S83.
2. **Radzina M**, Krumina G, Kupcs K, Miglane E. Should we use relative threshold values in CT perfusion for detection of early acute stroke? Cerebrovascular diseases 2012, Vol. 33, Suppl. 2, pp. 264-265.
3. **Radzina M**, Krumina G, Kupcs K, Miglane E. Brain perfusion correlation to ectracranial vessel stenosis, acute stroke study.Cerebrovascular diseases 2012, Vol. 33, Suppl. 2, p. 251.

Congress abstracts on research theme:

1. **Radzina M.,** Krumina G., Kupcs K., Miglane E. What is the role of extracranial carotid artery stenosis in evaluation of brain perfusion in acute stroke? European Congress of Radiology, 7-11 March 2013, EPOS poster Nr. C-1778, doi: 10.1594/ecr2013/C-1778. Vienna, Austria (poster).
2. **Radzina M.,** Krumina G., Kupcs K., Miglane E. Role of CT perfusion relative threshold values in diagnostics of acute stroke. European Congress of Radiology, 1-5 March 2012, EPOS poster Nr. 1069. Vienna, Austria (poster).
3. **Radzina M.,** Krumina G., Kupcs K., Miglane E. CT perfusion relative threshold values in acute stroke, Nordic Stroke Conference 28 Sep-1 Oct 2011, Tallinn, Estonia (poster).
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5. **Radzina M.,** Krumina G., Kupcs K., Dzelzite S., Miglane E., Millers A., Priede Z. (2010). MSCT imaging of brain perfusion in acute stroke. 3rd Baltic Congress of Radiology, 8-9 Oct 2010, Riga, Latvia (oral presentation).
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7. **Radzina M. ,** Krumina G., Kupcs K., Dzelzite S., Miglane E., Millers A. (2010). Brain perfusion disposition in acute stroke with known atherosclerosis of brachiocephalic vesels, use of multimodal computed tomography imaging. European Congress of Radiology, 4-8.March 2010, Vienna, Austria (poster).
8. **Radzina M.,** Krumina G., Pupols J. (2006). Multislice Helical CT angiography in diagnostics of intracranial and extracranial arterial dissection", 5th Baltic Congress of Neurology 02 Jun 2006. Riga, Latvia (oral presentation).

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1. Radzina M., Krumina G., Kupcs K., Miglane E.CT brain perfusion patterns in acute stroke with atherosclerosis of extracranial blood vessels. European Society of Neuroradiology Annual meeting, 2012.g.20-23.septembris, Edinburgh, United Kingdom (oral presentation).
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4. **Radzina M.,** Krumina G., Kupcs K., Miglane E. Role of CT perfusion relative threshold values in diagnostics of acute stroke. European Congress of Radiology, 1-5 March 2012, Nr. 1069. Vienna, Austria (poster).

5. **Radzina M.,** Krumina G., Kupcs K., Miglane E. CT perfusion relative threshold values in acute stroke, Nordic Stroke Conference 28 Sep-1 Oct 2011, Tallinn, Estonia (poster).

6. **Radzina M.,** Krumina G., Kupcs K., Dzelzite S., Miglane E., Millers A., Priede Z. MSCT imaging of brain perfusion in acute stroke. 3rd Baltic Congress of Radiology, 8-9 Oct 2010, Riga, Latvia (oral presentation).

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8. **Radzina M.,** Krumina G., Pupols J. Multislice Helical CT angiography in diagnostics of intracranial and extracranial arterial dissection", 5th Baltic Congress of Neurology 02 Jun 2006. Riga, Latvia (oral presentation).

Presentations in Latvian congresses and conferences on research theme:

1. 27.10.2012 – **Radzina M**. Computed tomography possibilities in diagnostics of acute stroke. 1st Latvian Stroke Congress, Riga, Latvia (oral presentation).

2. 04.10.2012 - **Radzina M**, Krumina G, Kupcs K, Miglane E. CT brain perfusion patterns in acute stroke, with atherosclerosis of extracranial blood vessels. Latvian Neuroradiology Society meeting, Riga, Latvia (oral presentation).

3. 29.03.2012 **- Radzina M.,** Krumina G., Kupcs K., Miglane E. CT brain perfusion patterns in acute stroke correlation to extracranial vessel stenosis. Rīgas Stradiņa universitātes 11. zinātniskā konference, 29-30 March, 2012, Riga, Latvia (oral presentation).

4. 26.11.2011 – **Radzina M.** Radiology examination role in emergency diagnostics. Latvian Medical Society Interdisciplinary conference 2011, Riga, Latvia (oral presentation).

5. 14.04.2011 - **Radzina M,** Krumina, Kupcs K, Miglāne E. CT perfusion relative threshold values in acute stroke patients. Riga Stradinš university 10th Scientific conference, 14-15 Apr 2011, Riga, Latvia (oral presentation).

6. 24.02.2011 - **Radzina M,** Krumina, Kupcs K, Miglāne E. Acute ischemic stroke multimodal CT imaging. Latvian Radiologist association conference, Riga, Latvia (oral presentation).

7. 24.11.2010 - **Radzina M**. Early ischemic stroke diagnostic possibilities. Latvian Neurologist society plenary meeting „New trends in neurology", Riga, Latvia (oral presentation).

8. 19.03.2010 - **Radzina M,** Krumina G. Multimodal CT protocol development for early acute stroke diagnostics and plannning for thrombolysis. Riga Stradinš university 9th Scientific conference, 18-19 Mar 2010, Riga, Latvia (oral presentation).

9. 02.11.2007 – **Radzina M,** Krumina G, Pupols J. Multislice CT angiography in intracranial and extracranial blood vessel dissection. New trends in imaging. RSU Radiology Institute 10th anniversary conference, Riga, Latvia (oral presentation).

10. 07.06.2006 – **Radzina M.** Intracranial and brachiocephalic artery dissection multislice CT imaging diagnostic possibilities, RSU Postgraduate education department student and resident scientific practical conference 2005/2006 New trends in medicine, Riga, Latvia (oral presentation).

11. 17.02.2006 - **Radzina M.** Brachiocephalic and intracranial blood vessel CTA. Case reports Latvian Neuroradiology society and Latvian Neurosurgery society joint meeting, Riga, Latvia (oral presentation).

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