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Clinical application of perfusion computed tomography in the early diagnosis of acute ischemic stroke and hemorrhagic transformation prediction

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Abstract

Background: Our study was designed to evaluate the efficacy of perfusion computed tomography (PCT) in patients with acute phase of stroke for the early diagnosis of this pathology and prediction of hemorrhagic transformation in the ischemic area.

Material and methods: We studied the functional PCT maps obtained at admission from 23 patients with acute ischemic stroke, compared to follow-up computer tomography or magnetic resonance imaging.

Results: Mean Transit Time(MTT) map showed that the highest sensitivity (80.3%) and parameters of relative Cerebral Blood Flow (rCBF) and Cerebral Blood Volume (rCBV) were the most specific (95.0% and 96.9%, respectively) in the early diagnosis of ischemic stroke. Automatic technique "Tissue Classification" showed the highest value of the overall accuracy (91.7%), a significant correlation with the final stroke extension and differentiation of potentially salvageable regions from the irreversibly damaged, which plays an important role in the treatment management. Evaluation of permeability function of the blood-brain barrier with a Permeability Surface area product (PS) showed high values of specificity, sensitivity and overall accuracy (89.5%, 75.0% and 87.0%) in the prediction ability of hemorrhagic transformation.

Conclusions: Quantitative analysis of functional parameters of dynamic cerebral perfusion computed tomography has significant efficacy in emergency diagnosis of acute ischemic stroke and hemorrhagic transformation prediction in tissue exposed to ischemia.

Key words: Computer tomography perfusion, acute ischemic stroke, hemorrhagic transformation, blood-brain barrier permeability.

Introduction

Stroke is the third leading cause of death in industrialized countries and the most frequent cause of permanent disability in adults worldwide [1, 2]. According to the American Stroke Association, every 45 seconds someone has a stroke, every 3 minutes someone dies of a stroke. According to this association 85 % constitutes ischemic stroke, which is the third leading cause of death (behind heart disease and all forms of cancer), leading cause of serious, long-term disability in the USA, where every year 700000 people experience a new or recurrent stroke, about 500000 are primary and 200000 are recurrent attacks and 40000 more women than men will have a stroke. One of the most undesirable complication of ischemic stroke is hemorrhagic transformation (HT), which may further complicate an already devastating clinical condition. HT after acute ischemic stroke is known to associate with poor outcome and delays the initiation of proper anticoagulation treatment, especially for stroke with cardioembolism [3]. Historically, hemorrhagic transformation, initially designated as "red softening," has long been recognized by neuropathologists to occur as a natural consequence of ischemic brain injury. To search for new treatments as well as intervention measures for HT, it is important to understand its underlying mechanism and identify its specific predictors [4].

CT is considered the gold standard in diagnostic imaging for the patients with acute stroke and the cerebral perfusion (perfusion computed tomography - PCT) is the most promising CT method in this regard. PCT is performed by the dynamic image acquisition and generates information, where the image intensity represents tissue density and changes depending on the time after intravenous injection of contrast agent. These data are used for calculating of the various perfusion-related parameters: cerebral blood flow - CBF, cerebral blood volume - CBV, mean transit time - MTT, time of local peak enhancement (TTP - time to peak) and capillary permeability (permeability surface - PS). Results are displayed in a graphic format (parametric images) as functional brain maps. These standard perfusion metrics are used to detect an acute ischemic stroke and the presence of "penumbra," the hypoperfused but potentially salvageable tissue at risk of infarction [5, 6, 7].

Tissue at risk of infarction (where the synaptic transmission stops with abolition somatosensory evoked potentials and installation of the electrical failure, but ischemic impairment is reversible even if lower paralysis starts) will have decreased CBF, normal or higher than normal CBV and increased MTT. On the other hand, infarcted tissue (synthesis of adenosine triphosphate is stripped out by demand and cell membrane pumps fail, causing efflux of K^+, influx of Ca^2, Na^+ and H_2O into neurons, causing membrane depolarization - at this point the damage is irreversible), or dying tissue (i.e. loss of auto-regulation) will show a different pattern: decreased CBF, decreased CBV and normal or slightly elevated MTT [8].

CTP, can not only provide the diagnostic information about ischemic region, but and the functional brain data about blood-brain barrier (BBB) physiology, especially its permeability. Microvascular permeability (expressed as the transendothelial transfer of constant or permeability surface area product [PS]) is a metric of BBB integrity.

Increased blood–brain barrier permeability, one of the pathological reactions following ischemic stroke, is believed to predispose to complications such as hemorrhagic transformation [9], massive vasogenic oedema, infarct expansion [10] and unfavourable clinical outcome [11, 12]. Like the standard

perfusion metrics, PS can also be calculated using dynamic imaging by measuring the leakage of an intravascular tracer (contrast agent) into the extravascular (interstitial) space [13, 14]. BBB permeability imaging provides a physiologic individualized measurement intimately connected to the underlying pathophysiology of hemorrhagic transformation (ischemia-induced vascular damage followed by reperfusion) and may, therefore, offer excellent sensitivity and specificity.

Although there are multiple multicenter studies in the world literature, demonstrating the effectiveness of CT perfusion in early diagnosis of ischemic stroke, cerebral perfusion in Moldova is not a part of the urgent investigation's list for these patients, causing the delayed diagnosis and initiation of specific treatment, such as thrombolysis. Our study is characterized by scientific novelty in the application of CT perfusion in assessment of BBB permeability in patients with hemorrhagic transformation phenomenon. It is not yet discovered, which imaging method has the highest predictive value in forecasting the hemorrhagic transformation of ischemic stroke. This research is the first neuroimaging study in Moldova with PCT application in patients with acute and hyperacute ischemic cerebral infarction with stratified analysis of sensitivity, specificity and accuracy for each functional map in correct stroke diagnosis and hemorrhagic transformation prediction.

Material and methods

Imaging data were obtained in emergency mode after anamnesis and clinical data collection at the admission to the Institute of Neurology and Neurosurgery (INN) (Chisinau, the Republic of Moldova); investigations were analyzed retrospectively. Informed consent was obtained from each patient or relatives or legal representative before the investigation with information about the benefits of the procedure, risks of introducing the contrast agent and the dose of ionizing radiation. The study included patients who underwent PCT and who met the following criteria: 1) age 18 years and more, 2) women of childbearing age who are not pregnant and not breastfeeding, 3) signs and symptoms suggestive of cerebral infarction (e.g. hemisensory disorders, hemiparesis, aphasia or visual field abnormalities) lasting up to 12 hours 4) no evidence of intracerebral hemorrhage, and 5) the patient underwent follow-up CT or MR imaging to confirm or rule out ischemic stroke.

Scanning Protocol. Brain PCT was performed at the Radiology Department of INN with the use of multidetector tomography equipment (64 slices) - VCT select (producer - General Electric Healthcare, USA) by dynamic scanning method (Cine Mode) with the administration of the contrast agent after non-contrast axial scan for the hemorrhagic stroke exclusion. Scanning parameters: tube rotation time - 1.0 seconds; the full length of rotation - 360 degrees; 5 mm slice thickness; the length of region covered by the dynamic scan - 40 mm; the overlap interval = 0.0 mm; total scan time - 40 seconds; active detector - central (20 mm); Gentry tilt - parallel to the orbital-meatal line, small field of view (25 cm); X-ray current voltage = 80 kV; current intensity - constant 150 mA; the total obtained number of primary images - 792. The scanning process started with 60 ml nonionic iodinated contrast Visipaque (iodixanol 320 mg/ml iodine concentration) automatic injection (Power Injector Nemoto with 2 syringes) in cubital vein at 4 ml/s flow rate, followed by administration of 40 ml saline at a rate of 4 ml/s. Multidetector CT technology allowed acquisition of four adjacent 5 mm thickness sections for each location. In most cases, the first section was localized on the basal nuclei and III ventricle's level (position above the orbits for the lens protection) with caudo-cranial data acquisition. The time before the contrast agent reached brain parenchyma allowed the base non-contrast images acquisition.

Data postprocessing was carried out after images transfer to the Advantage Workstation 4.6 (General Electric, Milwaukee, USA), using CT Perfusion 4 software - image analysis software package for dynamic stroke images assessment, protocol "Brain Stroke". Perfusion CT algorithm included image intensity quantification in CT image sets and the absolute values calculation in the following functional color maps: CBF - cerebral blood flow, mean transit time - MTT, CBV- cerebral blood volume, time to peak - TTP, and permeability surface area product - PS. General Electric CT Perfusion deconvolution algorithm is based on the convolution model. One of the inherent advantages of the convolution model is that it makes no assumption that the injection rate of the contrast agent, and subsequently the time it takes to reach its peak concentration in the vasculature, are nearly instantaneous or at least shorter than the minimum transit time of tissue, as other models do. Conversely, the convolution model takes into account the actual injection rate of the contrast agent, as determined from the time series data from a reference Region of Interest (ROI) located in an artery (arterial tissue density curve), when computing the quantitative values of perfusion parameters. Specifically, the algorithm "deconvolves" the arterial tissue density curve from the tissue density curve in each tissue voxel to compute an impulse residue function (IRF) from which the perfusion parameters are calculated. The perfusion parameters such as IRF T0, MTT, CBF, CBV and PS are derived from the tissue IRF, and, where applicable, are normalized to the pixel value associated with 100% of blood in a large vessel. The parameters are further normalized to the average tissue density, and hence, are expressed in their actual units of measurement per unit mass (e.g. BV is expressed in ml/100 g of wet tissue).

Cerebral blood flow (CBF) represents flow of blood through vasculature including conductance vessels (arteries, arterioles, capillaries, venules, veins, sinuses), being measured in ml/100g wet tissue/min. **Cerebral blood volume (CBV)** represents volume of blood in cerebral vasculature, being measured in ml/100 g wet tissue. **Mean Transit Time (MTT)** is the average residence time of contrast agent in a given tissue location. Mathematically, MTT is computed as the first moment of the IRF from IRF T0, and is displayed in seconds. In CT Brain Stroke, the calculated MTT is the sum of both the intravascular and extravascular contrast residence times (i.e. it incorporates the time interval required for the IRF to reach post-enhancement baseline). **Time-to-peak (TTP)** is defined as the time interval between the onset of the tissue enhancement and the peak of the tissue density curve. In practice, it is computed as the time interval between the last pre-enhancement image and the image with the maximum

intensity value. TTP is displayed in seconds. **Permeability Surface area product (PS)** is computed from the IRF, and is displayed in ml per 100g of wet tissue per minute (ml/100 g/min). The PS has the same units as CBF, as it quantifies the diffusion of some of the contrast agent into the interstitial space. It is used to assess the permeability of blood vessels. Permeability is related to the diffusion coefficient of the contrast agent through the pores of the capillary endothelium into the interstitial space due to the deficient or leaky blood brain barrier. It has also been linked to the diffusion of contrast agent through the large holes of the sinusoidal capillaries. In the tissue IRF, the contrast agent diffusion is related to the extraction fraction, or the fraction of contrast agent, which remains in the intravascular space after the initial IRF response and which then, diffuses exponentially into the interstitial space. **Tissue Classification** software analyzes the tissues affected by a stroke and is measured in ml/100 g of tissue. The input for this protocol is the computed maps of Average CBF and CBV. The tissue with blood volume below the threshold will be displayed in purple on blood volume map. The tissue with normal blood volume will be displayed in yellow on blood volume map.

The formal definitions of Blood Flow and Mean Transit Time assume that the injection of the contrast agent is instantaneous and there is no recirculation, which is not the case in clinical practice. This means that the algorithm must take into account the actual injection rate of the contrast agent to obtain *quantitative* results for CBF and MTT. For this purpose, the algorithm uses data from a reference ROI located in an artery to deconvolve the time course data and compute an *impulse residue function* (IRF) for each pixel location.

The statistical analysis included maps with absolute values - TTP, MTT, PS and relative values expressed in % of the affected region, compared with the healthy contralateral region (absolute value of healthy region is considered = 100%) - rCBF and rCBV and automatic computerized map Tissue Classification created by the software that reveals the penumbra regions and stroke by applying rCBF and rCBV thresholds [15, 16]. By this method, ischemic cerebral area (penumbra and infarction) has been defined to include cerebral pixel with decreased CBF > 34%, as compared to the corresponding region of healthy brain hemisphere, defined on the basis of clinical symptoms. In this selected region, pixels with values higher or less than 2.5 ml / 100 g were highlighted to differentiate penumbra and cerebral infarction [15, 16].

Data analysis was performed retrospectively individually for each functional map from 23 PCT investigations, performed on admission in INN. RCBV, rCBF, MTT, TTP, PS and Tissue Classification maps were analyzed, with registration of visual abnormalities in perfusion indices in four anatomical regions of the brain, according to Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke study (ATLANTIS) [17], plus 10 anatomic regions defined by the Alberta Stroke Program Early CT Score (ASPECTS) [18] and brain territories corresponding the vascularization of anterior cerebral artery (ACA) and posterior cerebral artery (PCA) in right and left cerebral hemisphere, with total of 32 territories. For ATLANTIS system pathological changes were assessed in four areas of the brain: 1) frontal, 2) temporal, 3) parietal and 4) basal nuclei area and insular cortex; were recorded with a score of 0-4. For ASPECTS system were assessed 10 areas of brain tissue, perfused by the middle cerebral artery (MCA), including the caudate nucleus, putamen, internal capsule, the insular region, M1, M2, M3, M4, M5, M6, were recorded with a score of 0-10 points (10 points maximum score indicating normal tissue).

The PCT maps evaluation consisted of their assessment by subjective visual comparison with the healthy hemisphere. Data were also analyzed using automated prototype software PCT (Tissue Classification, General Electric). As mentioned above, this software automatically builds a functional map of ireversibil cerebral infarction and penumbra areas, based on reference values of rCBF and rCBV. In this automatic computerized map was evaluated possible presence of penumbra/infarction in four ATLANTIS anatomical regions of the brain, 10 ASPECTS regions and ACP / ACA territories.

Blood-brain barrier permiability was analyzed on functional PS map from the "tumor perfusion" module of PCT 4 (General Electric) software, which calculates microvascular permeability and fractional blood volume based on the Patlak method [19]. PS color maps were not generated in time of initial assessment (on admission) and, therefore, had no importance in the treatment strategy selection (the fibrinolytic therapy administration) or subsequent clinical management. Patlak method is a two unidirectional compartments model which calculates PS by the linear regression. Each voxel of brain tissue contains 3 spaces: intracellular, intravascular (plasma) and extravascular (interstitial). Since iodinated contrast hydrophilic molecules (tracer) do not cross hydrophobic cell membrane and intracellular contrast agent enhancement can be ignored; only 2 compartments are considered (intravascular and extravascular).

The region of interest was traced individually ("freehand region"), for delineation of total tissue at risk of cerebral ischemia, based on the functional parameters abnormalities: increased MTT and decreased CBF. A copy region was reflected in the healthy hemisphere, being generated automatically by the PCT software for blood-brain barrier permeability assessment in contralateral normal brain tissue.

Absolute values of microvascular permeability were recorded, with the subsequent retrospective comparison of mean values in patient's group showed hemorrhagic transformation on follow-up brain CT and in group without this complication. To appreciate the true/false positive and negative results and calculating the sensitivity, specificity and accuracy, was used reference level = 2.3 ml/min/(100g), previously published [20] and validated to differentiate patients with possible hemorrhagic transformation (HT) of ischemic stroke.

According to the European Cooperative Acute Stroke Study "HT" was defined on non-contrast CT imaging as increased density area inside a hypodens region of typical vascular distribution [21]. Hemorrhagic transformation has been classified in two types: hemorrhagic infarction - HI and parenchymal hematoma - PH [21, 22, 23]. These forms have been subdivided into two types: HI 1 and HI 2, PH 1 and PH 2. HI1 are small peripheral petechiae in the ischemic region; HI2 – are confluent petechiae in the ischemic area, but without

mass effect. PH1 has been defined as intracerebral hematoma with mass-effect, occupying less than 30% of the ischemic region and the PH2 – hematoma, occupying more than 30% compared to the initial stroke volume.

CT or MRI follow-up images of each patient were analyzed according to the algorithm described above. In the follow-up investigation, performed a few days after onset of symptoms, final ischemic stroke region was recorded. The results were considered standard criterion for calculating the sensitivity, specificity and accuracy of PCT maps: rCBV, rCBF, MTT, TTP, and PS Tissue Clasification.

Results

We included in our study all the patients who underwent PCT investigation procedure described above in the INN radiology department with symptoms of acute stroke between January 2010 and January 2015. 23 patients met the inclusion criteria. Nine patients (9) were men and 14 women, with a mean age of 63.95 years (minimal age – 42 years and maximal age - 85 years). Clinical manifestations of stroke were recorded on the left side of the body in 16 patients and on the right side - in 7 patients. The average time from the onset of symptoms and the moment of PCT protocol was 6.6 hours, with a minimum of 1.0 and maximum of 12.0 hours.

A follow-up CT was performed in 21 patients (mean time from onset of symptoms to the follow-up imaging = 5,6 days, varying from 3 to 10 days). One patient was investigated by MRI (on the third day from the disease onset) including DWI (diffusion weighted imaging) and fluid-attenuated inversion recovery (FLAIR). In a patient with acute ischemic stroke with early extensive hemorrhagic transformation, follow-up investigation was not carried out, because of the extremely serious concomitant complications with consecutive death, which occurred 5 hours after admission. The final diagnosis was established as: ischemic stroke - in 21 patients (19 cases of non-lacunar stroke and two lacunar cases); transient ischemic attack (TIA) – in 2 patients. The region of the ischemic strokes had the following location: vascular region of anterior cerebral artery (ACA) - 1 patient, middle cerebral artery (MCA) territory - 14 patients, and posterior cerebral artery (PCA) region - 4 patients. Among the patients included in our study, 6 had suffered an ischemic stroke in the past, before the actual PCT procedure. Our control imagistic investigations revealed 4 patients with hemorrhagic transformation (HT) of the ischemic stroke. In 3 patients HT was detected 4-7 days after onset of clinical symptoms; in a patient early haemorrhagic transformation was registered (at hospital admission - 1 hour after onset of symptoms). According to ECASS II classification of HT, 1 patient presented HI type 2 of HT; 2 patients – PH type 2 and 1 patient – PH type 1. Male / female ratio was 3/1, but the small number of patients with hemorrhagic transformation determined impossibility of epidemiological data appreciation in this research group.

The sensitivity, specificity and precision of the PCT data in the ischemic stroke assessing are displayed in **Table 1**. The general precision of the PCT maps in the infarct region detecting in acute ischemic stroke was up to 86.6%, and overall accuracy of PS in predicting hemorrhagic transformation of ischemic strokes - up to 87%. The TTP and MTT maps (79.4% and 80,3%, respectively) were significantly more sensitive than rCBF and rCBV (67.3% and 57,1%, respectively). The sensitivity of the automatic classification of the lesion tissue (Tissue Classification) was 72.3%, which is close to average sensitivity of PCT maps (71.3%). rCBF and rCBV (95.0% and 96,9%, respectively) showed significantly higher specificity than the TTP and MTT (81.3% and 82.3%, respectively).

The automatic method for tissues classification showed very high specificity (96.6%), broadly similar with the rCBV map specificity (96.9%). The blood brain barrier permeability PS map showed both high sensitivity and specificity (75.0% and 89.5%, respectively) for hemorrhagic transformation prediction. The overall PCT maps accuracy in the early diagnosis of ischemic stroke presented a range of values between 81.0% and 91.7%. rCBF and rCBV showed an important overall accuracy (89.5% and 89,0%, respectively), significantly higher compared with TTP and MTT parameters (81.0% and 81.9%, respectively). The automatic algorithm Tissue Classification for cerebral ischemia region delimitation showed the highest value of the overall accuracy (91.7%).

False-negative PCT results were generally related to the lack of spatial coverage. PCT failed to fully reveal non-lacunar stroke only in one case from 23, which was identified by

Table 1

Sensitivity, specificity and overall accuracy of CT perfusion in patients with acute ischemic stroke

	True-pozitive (TP)	Fals-pozitive (FP)	Fals-negative (FN)	True-negative (TN)	sensibility TP/(TP+FN)	specificity FN/(TN+FP)	overall accuracy (TP+TN)/(TP+TN+FP+FN)
TTP	116	110	30	480	79,4%	81,3%	81,0%
MTT	118	104	29	485	80,3%	82,3%	81,9%
rCBF	99	29	48	560	67,3%	95,0%	89,5%
rCBV	84	18	63	571	57,1%	96,9%	89,0%
tissue classification	107	20	41	568	72,3%	96,6%	91,7%
average					71,3%	90,4%	86,6%
PS (HT)	3	2	1	17	75,0%	89,5%	87,0%
736							

control MRI in the brainstem region. This anatomic region, usually, is not included in the PCT scanning surface because it requires the inclusion in the irradiation region of the lens and may cause artifacts produced by the bones from the skull base. In 2 cases, follow-up imaging showed lacunar strokes that were too small to be detected by the PCT maps. The other false-negative cases were false negative regions in patients with true-positive pathologies in which PCT has identified most, but not all ischemic areas. In one case, surprisingly, in the region in which control imaging showed cerebral infarction, PCT revealed hyperemia (high rCBF and rCBV, low MTT and TTP), but not oligemia. This result was included in the list of false-negative cases in accordance with the used evaluation criteria. Similar situation was observed in 2 patients with transient ischemic attack (TIA) like final diagnosis. This fact should be considered in future studies. Finally, in 2 patients, PCT maps were of poor quality due to motion artifacts which created difficulties in detecting oligemia in some areas. We included these results in false-negative category.

A case of arterial recanalization was also documented. In this case, the rCBF, MTT and TTP maps showed abnormalities in some areas, which were not confirmed as ischemic region in the control investigation. The automated computerized map described these areas as "penumbra". PCT false-positive results were recorded in 2 cases of TIA, where TTP and MTT maps showed a pattern suggestive of ischemia. Old infarcts also gave false-positive results because they can be differentiated from acute stroke only when PCT maps are interpreted in comparison with non-contrast CT in the corresponding region.

PS showed an increased permeability of the blood-brain barrier (BBB) in 5 patients from the total study group (23 patients), only in 3 of them hemorrhagic transformation (HT) was recorded. According the HT ECASS II classification, 2 patients presented "parenchymal hematoma (PH)" type 2 and 1 patient - PH type 1. In 2 other patients with increased permeability of the BBB, the control investigation (false-positive results) revealed massive stroke development occupying an entire cerebral hemisphere with extensive cerebral edema, complicated with the opposite part shift of middle cerebral structures, brain tissue herniation through the foramen magnum with subsequent significant deterioration of the neurologic state and vital parameters and death. The permeability of the BBB in ischemic stroke region on the PS map in patients with hemorrhagic transformation HI type 2 did not exceed the given reference level (false-negative results), but the native CT control investigation, realized 4 days after the symptoms onset, showed hyperdense regions of HT. In 17 patients we detected lower values than the given reference level for the BBB permeability, but the control CT didn't identify HT. This group of patients formed the true-negative group for the PS map.

Discussion

After analyzing the obtained data, we found that the dynamic PCT examination had high sensitivity, specificity and general accuracy in detecting acute ischemic stroke within less than 12 hours from symptoms onset. TTP and MTT maps (79.4% and 80.3%, respectively) were significantly more sensitive than rCBF and rCBV (67.3% and 57.1%, respectively), but rCBF and rCBV were significantly more specific (95.0% and 96.9%, respectively). The automatic method Tissue classification showed the highest overall accuracy (91.7%), very high specificity (96.6%) and average sensitivity (72.3%). Example of PCT investigation of acute ischemic stroke with 2 follow-up non-contrast CT is shown in Figures 1 and 2.

The role of PCT maps in the assessment of cerebral perfusion in comparison with other imaging methods. Realization of accurate quantitative PCT maps, through deconvolution method, was validated in a number of studies, which evidenced the high specificity and sensitivity of this imaging method [24-32]. Validation was performed by comparison with Xenon Computer Tomography (XeCT) [28, 33], Positron Emission Tomography (PET) [34] and Magnetic Resonance Perfusion (MRP) [35-38], both in experimental and clinical studies [24,25,27] .

According to other study results [39], the correlation between MRP and PET perfusion values was not as suggestive as it was expected. Perfusion CT has a higher spatial resolution and it is easier to be quantified than MR perfusion. Also, MRP may be more sensitive to contamination by large vessels artifacts. These factors may contribute to the possibility that visual assessment of ischemic core / penumbra region to be more accurate using PCT than MRP [40, 41]. Moreover, if to exclude the vascular pixels from the CT-CBF calculation, quantification of the mean CBF is very accurate, compared to the obtained values by $H_2{}^{15}O$ positrons in PET investigation [42].

When compared with MRP, PCT has the advantages on increased speed of realization, lower cost, and, the most important, the wider availability. PCT functional parameters (CBV, CBF and MTT) can be easier quantified than their similar MRP values, explained, partially, by the linear relationship between the concentration of iodinated contrast agent and the CT image density (Hounsfield units), a relationship which can't be attributed to gadolinium concentration and MRI signal intensity. However, as other techniques with the use of the bolus of contrast, the quantification depends on the deconvolution method, used for CBF calculation, which compares the curve based on the contrast enchancement in the tissue and the intra-arterial appearance of the contrast agent. Due to its availability, simple methodology and quantitative results, CTP has the potential to extend patients access to new treatment strategies and clinical studies based on imaging methods. A current disadvantage of the CTP method is the limited scanning region, which depends on the manufacturer and the CT scanner generation. Many contraindications for MRP examination, including difficulty of scanning of patients with installed monitors or artificial ventilation, the presence of cardiac pacemaker or implantable defibrillators, the risk of aspiration during the long supine position and the difficulty to obtain historical data to exclude metal implants, are absent in case of CTP examination.

In our study the highest sensitivity was registered for MTT map due to the presence of 118 true-positive areas identified on this map.

PCT false-negative results were related, mostly, to the lack of spatial coverage, which has been reported for other

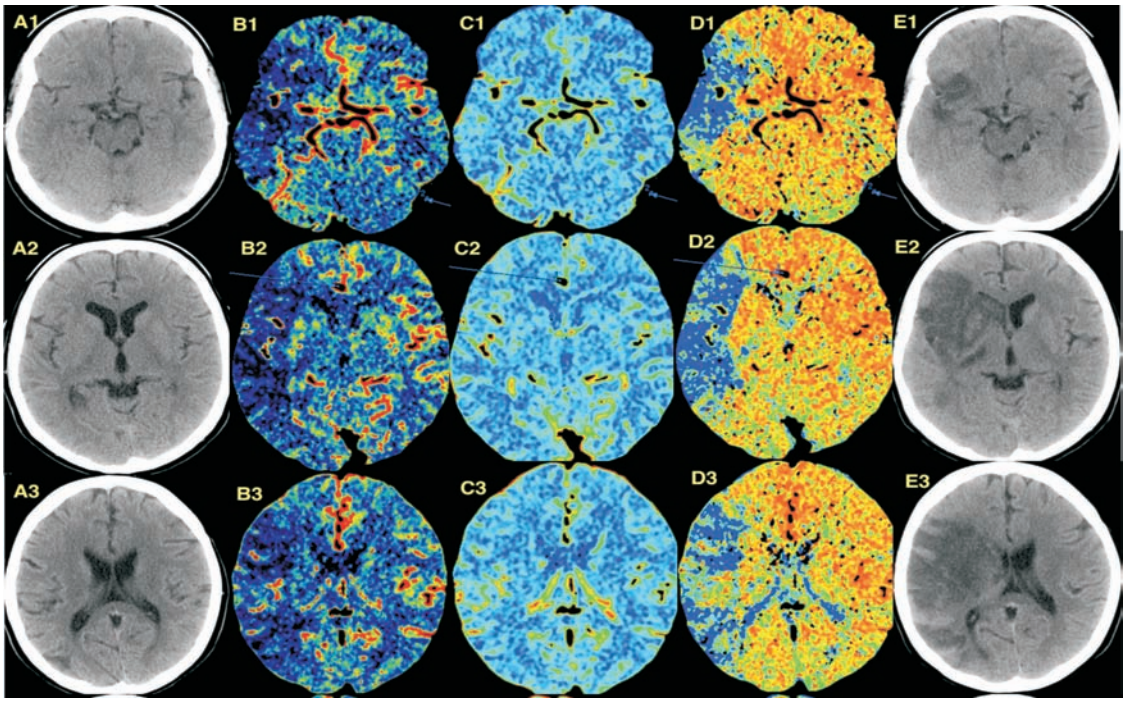

Fig. 1. Female patient, 40 years old with known history of arterial hypertension (grade III) and diabetes type 2, presented in emergency department of INN with left hemiparesis. A1, 2, 3 – non contrast CT, 2 hours after symptoms onset – there are no signs of abnormalities. B, C, D – PCT investigation (2 hours after symptoms onset). An extensive area of cerebral hypoperfusion in the right middle cerebral artery vascularization territory. B1, 2, 3 – rCBF map. C1, 2, 3 – rCBV map. D1, 2, 3 – MTT map. E1, 2, 3 – non contrast CT follow-up investigation on 4th day after symptoms onset. An extensive area of cerebral ischemic infarction in the right middle cerebral artery vascularization territory, diffuse right hemisphere edema with compression of the right lateral ventricle.

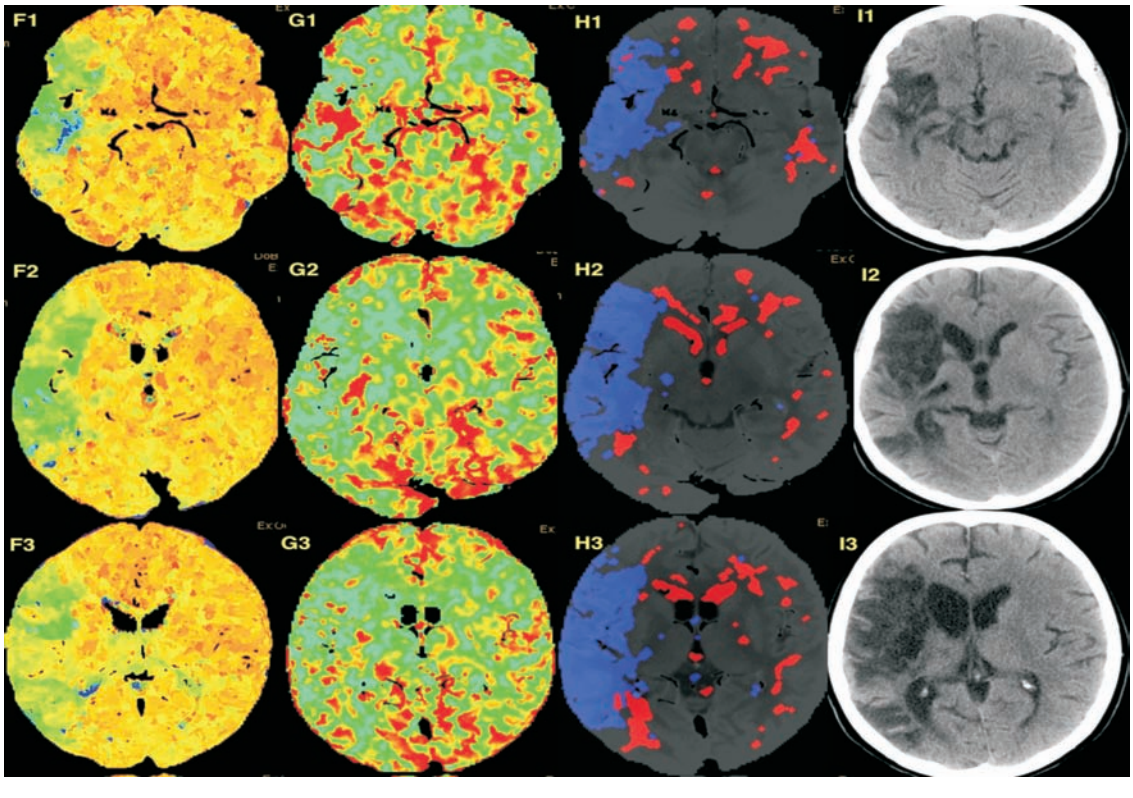

Fig. 2. The same patient. F, G, H – continuation of PCT investigation. F1, 2, 3 – TTP map. G1, 2, 3 – PS map. H1, 2, 3– automatic Tissue Classification map, blue zones correspond the irreversible infarcted tissue, red zones correspond to "penumbra". I1, 2, 3 – non contrast CT follow-up investigation after 6 months, chronic stage of ischemic stroke, massive cystic-gliotic changes in the right middle cerebral artery vascularization territory with retraction of the right lateral ventricle.

PCT dynamic techniques [43, 44]. We also identified false-negative areas in patients with true-positive pathology (e.g., PCT showed majority of ischemic areas, but not all). Some lacunar strokes were not identified on the PCT maps, due to the lack of spatial resolution. In 1 patient, we identified the pattern that was included in the group of false-negative results based on the classification algorithm used in our study. This case showed hyperemia (high rCBV and rCBF, low MTTs and TTP), but not oligemia in a territory where control investigation showed the formation of cerebral infarction. This situation was probably related to the so-called "luxury perfusion" and should be considered in future studies.

The majority of false-positive PCT results were associated with TIA. In case of TIA, MTT is prolonged but rCBV is also increased, probably due to insufficient circulation and cerebral vascular autoregulation with subsequent preservation of rCBF. PCT false-positive results were also recorded in case of subacute and chronic infarcts, which usually have the same PCT characteristics as acute strokes (extended TTP and MTT, reduced rCBF and rCBV). Subacute and chronic infarcts are easily distinguished from the acute one (less than 12 hours from symptoms onset), based on CT scan without contrast. In this study, non-contrast CT was not assessed, which increased the number of false-positive PCT results. We couldn't appreciate the impact of combinative evaluation of non-contrast CT investigations and PCT maps, but it is likely to reduce the number of false-positive cases.

Clinical interpretation of PCT data should include evaluation of sensitive and specific maps for screening of patients with acute cerebral ischemia. MTT and TTP maps are extremely sensitive for detecting ischemia. TTP map is also sensitive in the detection of intracranial or extracranial vascular stenosis, independently of cerebral ischemia. That is why MTT map is more useful in ischemia screening, considering that it doesn't highlight stroke only, but TIA also. rCBF and rCBV maps are the PCT maps with the highest specificity and their combined interpretation by the automatic computerized method has an accuracy of 91.7%. In our study, not all patients were investigated by the follow-up CT-angiography; therefore it was impossible to systematically assess the correlation of recanalization or persistent arterial occlusion and also the resolution of penumbra or the increase of ischemia region over penumbra with PCT maps precision.

We have not performed an interpretation which combines various PCT maps, but we can assume that the sensitivity and specificity of PCT maps associated with non-contrast CT investigation analysis can be considerably higher when using MTT to identify ischemia and rCBF and rCBV maps to confirm the diagnosis in areas with prolonged MTT. In addition, the integration of CT angiography results (CTA) could increase this accuracy and could be the subject of further studies. Most patients in our study had clinical suspicion of hemispheric stroke, limiting the number of patients with lacunar stroke or other small strokes and lesions in the posterior fossa. The PCT technique is limited in the diagnosis of posterior fossa lacunas and bigger strokes because of the limited spatial resolution and artifacts from this region. Another limitation of our study is the requirement of control scanning for enrollment. This criterion excludes a large proportion of patients with TIA and perhaps the assessment of accuracy by reducing non-stroke patients.

In our study of PCT maps analysis in the acute stage of ischemic stroke, four patients developed hemorrhagic transformation in the evolution of the pathology, which allowed the retrospective assessment of the blood-brain barrier permeability through analysis of Permeability Surface area product (PS). PS showed high specificity, sensitivity and overall accuracy (89.5%, 75.0% and 87%, respectively) in prediction of hemorrhagic transformation. Cerebral microvascular permeability research was considerably limited because of the very small group of patients (4 persons). Our results require validation in larger groups of patients, with the whole spectrum of HT forms (4 types of HT). However, despite the small group of patients, our results correspond to previously published studies.

A recent study [45] has demonstrated a difference between PS values in HT and non-HT groups. The authors confirmed that any PS values from 6.0 to 9.8 ml / 100 mg per minute can be used as a threshold value for HT prediction with 100% sensitivity and specificity. The authors showed that elevated PS may be evidenced in the hyper-acute period of the ischemia using dynamic PCT data of the contrast first-passage. Patients with high PS and who haven't been treated with recombinant tissue plasminogen activator (rtPA) developed asymptomatic, small infarcts (hemorrhagic petechia). Christopher D. d'Esterre (2013) has showed that patients with HT presented significantly higher PS values than the group without hemorrhagic transformation. A reference PS value of 0.23 $ml^{-1} \bullet min^{-1} \bullet (100g)^{-1}$ differentiated HT group from the non-HT group [46]. Their results showed that, in addition to the PS parameter and the ASPECTS score, other factors (age, gender, or NIHSS score at baseline) were not associated with HT. Hom J. et al. investigated the CT perfusion possibilities in predicting HT and malignant edema in patients with acute ischemic stroke [47]. Researchers have reported that the use of perfusion BBB values above the mentioned threshold, like single predictor of HT, has a sensitivity of 100% and a specificity of 79% (5 false-positive results from 32).

Other functional CT perfusion parameters have been also studied to determine the correlation with HT, but the results showed no statistically significant difference, excepting rCBV map. Patients with HT presented a larger mean total volume of cerebral tissue at risk of ischemia, a prolonged rMTT and a reduced rCBF, when compared to the control group, although these parameters showed no significant statistical difference. The persons with HT had a mean rCBV significantly lower than the control group ($p = 0.01$). Consecutively, with every 0.1-U decrease in rCBV, the risk of HT increases by 14% [48]. Prediction of HT, by reduced pretreatment CBF, was first proposed by Ueda et al. with the use of SPECT [49]. A 50% reduction from the normal value of the CBF was considered as critical value for the HT development [50]. Gupta et al., in their study including 23 patients with stroke or symptomatic carotid stenosis, have concluded that ipsilateral CBF average of 13 ml / 100 g per minute was an indicator for the development of HT [51]. In another cohort, they found that rCBV, but not rCBF, was a stronger predictor of HT. These results are similar with other studies where rCBV (but not rCBF) is a strong predictor of the penumbra viability in acute ischemic

stroke patients [52], with similar values [53] or even lower [54] than those reported by the authors for patients with HT. Therefore, the penumbra viability indicators can indirectly predict the HT, which occurs more often in the infarct core region than in the irreversible penumbra part. Jain et al., found that rCBV level of at least 0.98 can predict the development of HT in stroke patients, with 72% specificity [48].

Our study's design did not include analysis of other PCT parameters (excepting PS) as predictive factors for potential hemorrhagic transformation, remaining the subject for further studies.

Conclusions

Quantitative analysis of functional parameters in dynamic cerebral perfusion computed tomography is very effective in the emergency diagnosis of acute ischemic stroke and hemorrhagic transformation prediction. Mean Transit Time map showed the highest sensitivity, relative Cerebral Blood Flow and relative Cerebral Blood Volume parameters were the most specific in the early diagnostic of ischemic stroke. The automatic method Tissue Classification showed the highest overall accuracy, significant correlation with final ischemic region extension, stratification of recoverable regions (penumbra) and constantly affected areas – facts, which are very important in treatment strategy selection. Assessment of blood-brain barrier permeability functions by analyzing the Permeability Surface area product, showed high specificity, sensitivity and overall precision in the hemorrhagic transformation predictive ability.

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