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Review

CT Perfusion – an Up-to-Date Element of the Contemporary Multimodal Diagnostic Approach to Acute Ischemic Stroke

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Abstract

Acute ischemic stroke is of great clinical and societal importance due to its high incidence and mortality rates, as well as the fact that those who are affected suffer from permanent acquired disability. Modern trends explicitly state that the disease's diagnostic plan should use a multidisciplinary approach. The therapeutic steps that ultimately determine the clinical outcome are defined by an accurate diagnosis of acute ischemic stroke. Highly specialized facilities for the diagnosis and treatment of acute ischemic stroke (Stroke Units) are in operation in countries that make significant investments in healthcare. Imaging the brain parenchyma at risk, or the so-called ischemic penumbra, in acute ischemic stroke is one of the main tasks of the multimodal computed tomography approach. The most rapid method for imaging the ischemic penumbra is computed tomography perfusion (CTP). This modality provides information about the anatomy and the physiologic state of the brain parenchyma.

The current literature review offers a comprehensive overview of the various aspects of computed tomography perfusion in acute ischemic stroke and, more specifically, about the differential diagnosis of acute ischemic strokes and diseases that mimic strokes, predicting the risk of hemorrhagic transformation, the computed tomography perfusion used in intravenous thrombolysis (IVT) beyond the therapeutic window, wake-up strokes (WUS) and strokes of unknown onset (SUKO), and the reported predictive parameters of CTP in correlation with the clinical outcome in acute ischemic stroke.

Keywords

CT perfusion, intravenous thrombolysis, ischemic stroke, neuroimaging, penumbra

INTRODUCTION

In developed countries, there has been a noticeable decline in the incidence and mortality rate of ischemic strokes over the past few decades. The basis of these results stems from the reported improvements in the organization and implementation of primary and secondary prophylaxis of the disease, as well as the introduction of new trends in pharmacotherapy modern neurorehabilitation of acute ischemic stroke. Regardless of the efforts done, cerebral infarction remains the second most common cause of death (11%) and the leading cause of disability worldwide.[1] In our country, according to data from the National Statistical Institute, the mortality rate of cerebrovascular disease is 339.5 (average for both genders) per 100 000 people. [2] These statistics point to an immediate response from

healthcare authorities in terms of taking decisive action in line with what has been done worldwide to control the process, which affects not just the elderly population.

Worldwide, in recent years, the diagnostic multimodal computed tomography approach in established stroke centers (including native CT, CT-perfusion, and CT-angiography) has become more widely available due to the speed of achieving positive results in neuroimaging of the cerebrum, especially in the development of impaired cerebral perfusion.

The interest and commitment of the neurological community in our country to apply this methodology in emergency centers became the reason for the present review. A review of the basic technical data on the computed tomography perfusion (CTP) method was performed as an up-to-date element in the multimodal diagnostic approach to acute ischemic strokes, including the various aspects of its application and, above all, its significance in reporting the penumbra-verifying parameters in acute ischemic stroke, as well as defining possible perspectives for future studies on the subject.

Diagnostic significance of the penumbra in acute ischemic stroke

Brain tissue is extremely sensitive to ischemia due to the lack of energy reserves. In limited (or completely blocked) blood flow, neuronal vitality may be sustained for about 2-3 minutes. In an acute ischemic stroke, the ischemia is often incomplete – the affected brain tissue receives collateral blood flow through intact arteries. In those cases, neuroimaging shows a central focal area with irreversibly infarcted tissue (infarct core), surrounded by a peripheral area of hypoperfusion, called penumbra (derived from Latin '*paene,*' meaning 'almost,' and '*umbra,*' meaning 'shadow'). In the penumbra zone, the elements of the brain parenchyma, mesenchymal and glial stroma are preserved.[3] The first definition of the ischemic penumbra was given by Astrup and Simon in 1981: "an area of impaired cerebral blood flow (CBF) with absent spontaneous or induced electrical potentials which has preserved ionic homeostasis."[4] This forms the core of the idea that the penumbra is ischemic brain tissue that can potentially be salvaged with timely restoration of perfusion.

The ischemic penumbra has been the subject of scientific research for the past 40 years. The most expedient method for its imaging is through CT perfusion. This imaging in the acute period of ischemic stroke is of crucial importance for selecting patients who meet the criteria for effective reperfusion therapies. When comparing standard clinical predictive markers of outcome such as "time since incident onset" with CTP biomarkers – "ischemic core and penumbra volume", it turns out that the latter are much more accurate predictive indicators that could be used as prognostic markers after reperfusion therapy.[5] Despite improvements in neuroimaging modalities, there is still no gold standard regarding the identification of the ischemic core and penumbra, and no consensus has been reached on widely available and accurate imaging biomarkers with prognostic significance.

CTP – the chronological clock versus the 'tissue clock'[6]

The CT-perfusion study of the brain provides information on hemodynamic parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) which can precisely identify the infarct core and penumbra.[7] The reported sensitivity of CTP in the diagnosis of ischemic stroke is 82% and the specificity is 96%. These data demonstrate the method's superiority to native CT and bring it closer to CT angiography's imaging capabilities.[8] CTP is a contrast study that monitors only the first passage of the iodinated contrast agent through the cerebral circulation. The technical execution time is about 45 seconds, and the volume of the necessary contrast agent – about 50 ml. Colored perfusion maps are obtained, showing verification curves of CBV, CBF, MTT, time to peak (TTP), and time to maximum (Tmax) parameters **(Fig. 1).** The accuracy of the method has been confirmed by comparison with other perfusion techniques such as positron emission tomography (PET).[9]

Based on the CTP study, curves were generated that show a correlation between the transit time of the contrast through the brain tissue and the attenuation. For this purpose, it is necessary (ideally – manually) to select so-called 'regions of interest' (ROI) represented by an area of an arterial and venous vessel. The arterial ROI is optimally an unaffected vessel that runs perpendicular to the plane of examination – one of the two anterior cerebral arteries, the contralateral middle cerebral artery, or the internal carotid artery. An inappropriate choice of artery results in higher MTT values and lower CBF values. In an emergency, one of the two anterior cerebral arteries (A2-segment) is chosen due to their already proven accuracy in numerous studies. [9] The venous ROI is often the superior sagittal sinus or the torcula Herophili. Incorrect choice of venous vessel leads to increased values of CBV and CBF. A detailed review of all images is appropriate before selecting suitable vascular areas. Otherwise, the study may be uninformative. The passage of the contrast agent through the brain tissue and the resulting transient hyper-attenuation (proportional to the amount of contrast agent in the vasculature of the study area) are the basis for the generation of the 'time-attenuation' curves for the arterial-venous ROI **(Fig. 2)**.

As a result of the study, we obtained the following numerical values of the parameters:

Time to maximum (Tmax, delay time) – the delay, expressed in seconds, that the contrast agent takes to reach the ischemic zone. It is calculated by the deconvolution method. It is analogous to TTP. It is stated to represent one of the most accurate indicators for the precise evaluation of the ischemic area.[11]

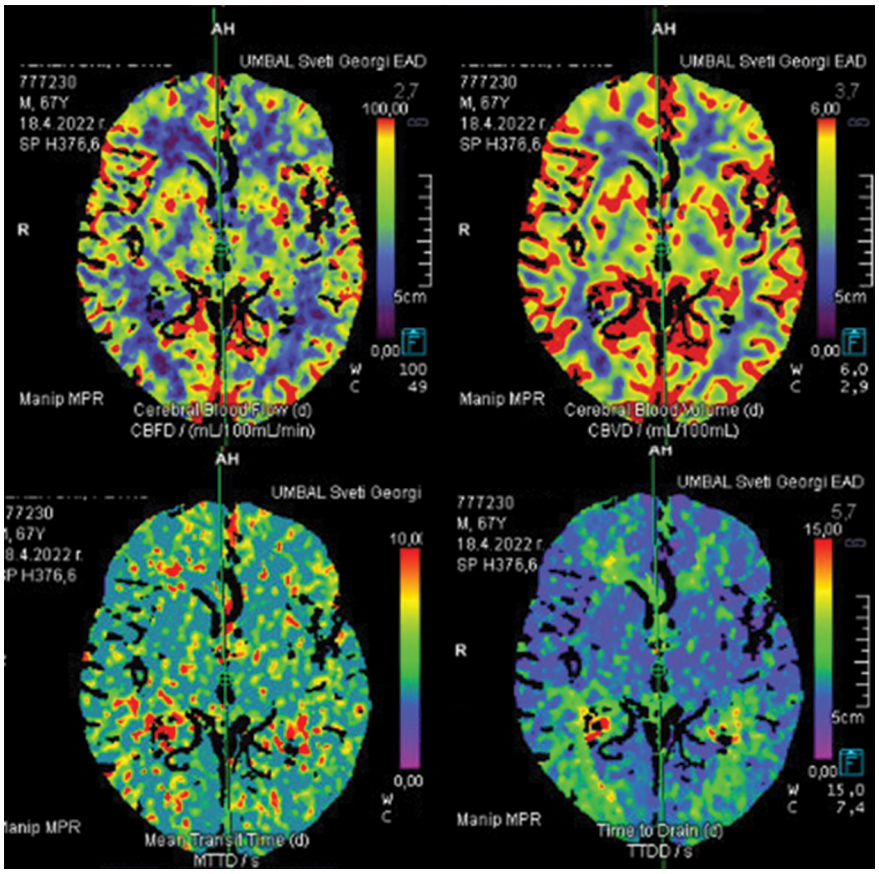

Figure 1. Normal CTP maps of a healthy individual.

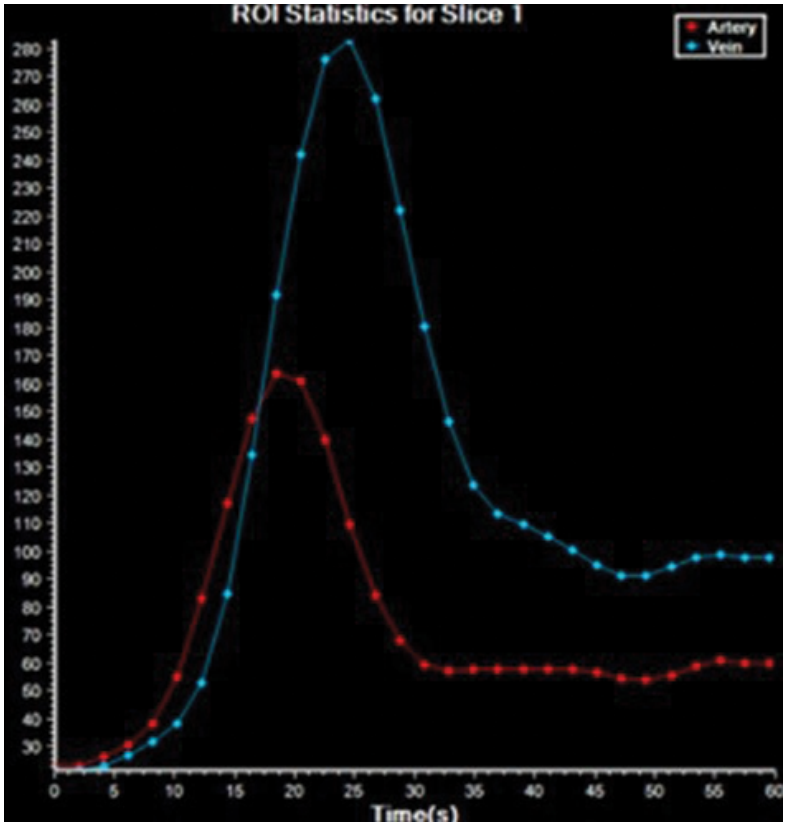

Figure 2. A typical curve 'time-attenuation' generated in CTP. In red – the arterial curve, and in blue – the venous one.[10]

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Time to peak (TTP) – the time from the beginning of the conducted study to the achievement of the maximum intensity of contrast medium in each voxel.

Mean transit time (MTT) – the time required for the contrast agent to reach the venous vessels by passing first through the arteries and capillaries. With delayed blood flow, this time is prolonged by secondary vasodilatation.

Cerebral blood flow (CBF) – a unit of blood volume that passes through 100 grams of brain tissue per unit of time. It is measured in milliliters per 100 grams per 1 minute. In the infarct core, this parameter is reduced by about 30%.

Cerebral blood volume (CBV) – the volume of blood that is found in 100 grams of brain tissue.[7]

As a result of numerous studies, the normal values of CT-perfusion parameters, as well as their changes in ischemia and necrosis of the brain parenchyma, have been reported **(Table 1)**.

The registered parameters of CT-perfusion in acute ischemic stroke have different pathological characteristics in correlation with the penumbra and the necrotic zone.

Table 1. Normal values of CT-perfusion parameters[12]

Brain tissue	CBF	CBV	MTT
Grey matter	60 ml/100 g/min	4 ml/100 g	4 s
White matter	25 ml/100 g/min	2 ml/100 g	4.8 s

1. In the presence of complete ischemia without a formed infarction, prolonged TTP, MTT, Tmax, and reduced CBF are visualized, while CBV is normal or increased in functional autoregulatory mechanisms.[7]

2. In the presence of a small infarct core and a large ischemic area, CTP finds reduced CBF and CBV in the infarct core, and in the area around it – prolonged MTT, TTP, and Tmax, with preserved CBV. This combination of CT-perfusion parameters is consistent with a large area of potentially salvageable ischemic penumbra. In the absence of contraindications, those patients are indicated for reperfusion therapies with expected good clinical outcome[7] **(Fig. 3)**.

3. In the presence of a large infarct core and a small ischemic area, CTP establishes a large area of reduced CBV corresponding to the size of the infarct core and a small area of prolonged MTT, TTP, and Tmax, as well as preserved CBV corresponding to the ischemic penumbra. In those patients, reperfusion therapies are not appropriate, and the risk of complications is high.[7]

4. In the presence of a complete infarction, an area of reduced CBV and CBF and prolonged MTT, TTP and Tmax is observed with no other zone surrounding it. Those patients would not benefit from reperfusion therapies, and the risk of complications (mainly intracranial hemorrhage) is unreasonably high.[7]

Several studies support the fact that the CBV perfusion map imaging the area of the infarcted core correlates

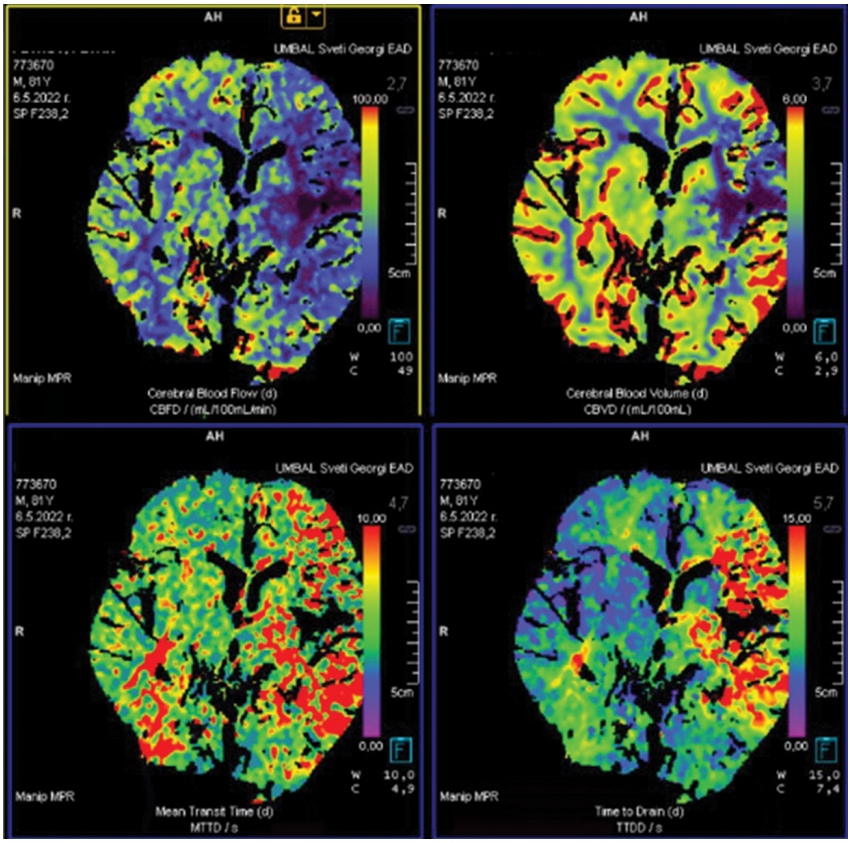

Figure 3. CTP map of an 81-year-old patient showing a penumbra engaging the entire territory of the middle cerebral artery with a small infarct core.

with DW-MRI images.[13,14] The penumbra is characterized by increased MTT, decreased CBF, normal or slightly increased CBV (due to secondary auto-regulatory mechanisms and early stages of ischemia). The infarct core is characterized by a marked decrease in CBF and an increase in MTT, with a decrease in CBV. The size of the penumbra zone is estimated by the equation: Penumbra = Cerebral blood flow – Cerebral blood volume, or Penumbra = Mean transit time – Cerebral blood volume.[7]

According to the clinical study of Srinivasan et al.[15], the MTT map is considered the most sensitive for detecting ischemia, while CBF and CBV are more sensitive for distinguishing the penumbra zone from the complete infarction zone.

In a study by Wintermark et al.[16], CTP was found to be a more accurate method than native CT for the detection of ischemic stroke (75.7%-86% vs. 66.2%, $p<0.01$). MTT maps are more sensitive, while CBF and CBV are more specific for detecting an infarcted area.

Computed tomographic perfusion as a method for detecting diseases mimicking stroke – stroke mimics

Approximately 20% of patients presenting to emergency departments with suspected ischemic stroke are affected by conditions that mimic stroke. Epileptic seizures are the most common stroke mimics.[17] When prolonged or forming status epilepticus, the most common CTP finding is focal cortical hyperperfusion. In the postictal period, a normal CTP image is observed, and less often – focal hypoperfusion of the cerebral cortex and underlying subcortical white matter.[18] In patients with epileptic seizures, local hyperperfusion is associated with recent or ongoing epileptic activity, while hypoperfusion may be postictal or accompany cerebral infarction.[18] These findings are confirmed by another study with CTP that included 43 patients with suspected acute cerebral infarction who were subsequently diagnosed with focal epileptic seizure with or without acute ischemic stroke.

Another retrospective study also analyzed CTP data in patients with suspected cerebral infarction. The 37 included patients with suspected ischemic stroke were subsequently diagnosed with another disease, most often – an epileptic seizure. All patients underwent electroencephalography and CTP. Cortical hyperperfusion was found in most of them by CTP.[19]

Computed tomographic perfusion as a method for assessing the risk of hemorrhagic transformation of cerebral infarction

Hemorrhagic transformation of acute ischemic stroke is a complication that is reported in 2.2%–44% of clinical cases and 70% of autopsied patients.[20]

CTP provides an opportunity to measure the permeability of the blood-brain barrier (BBBP). A retrospective study of 32 acute ischemic stroke patients who underwent CTP and had the blood-brain barrier's permeability measured before beginning reperfusion therapy found that the BBBP parameter was 100% sensitive and 79% specific in predicting the risk of symptomatic hemorrhagic transformation and malignant edema.[21]

A meta-analysis including 15 studies has examined the same correlation concluding that the indicator BBBP had 84% sensitivity and 74% specificity regarding the prediction of the risk for hemorrhagic transformation of the ischemic lesion.[22]

CTP-based intravenous thrombolysis (IVT), performed beyond the therapeutic window in patients with acute ischemic stroke

Intravenous thrombolysis with tissue plasminogen activator is a safe and effective therapeutic method in acute ischemic stroke treatment up to 4 and a half hours after the onset of the neurological symptoms.[23] Modern perfusion neuroimaging techniques allow selection of patients with acute ischemic stroke indicated for reperfusion therapy beyond the therapeutic window.

The incidence of hemorrhagic transformation was similar in the two groups, according to a prospective study that included 215 patients and divided them into two groups: those treated with IVT within the therapeutic window up to 4 hours and a half after stroke onset (n=172), and those treated after the therapeutic window after performing CTP (n=43) (2.9% in the first group and 2.3% in the second; $p=1.0$). Despite the lower rates of recanalization of middle cerebral artery after 2 hours in the second group, it proves the diagnostic value of CTP for the triage of patients admitted beyond the therapeutic window.[24]

According to the DAWN and DEFUSE 3 studies, patients with acute ischemic stroke would benefit from the effects of reperfusion therapy (thrombectomy) within 24 hours of stroke onset, performed after precise selection based on perfusion imaging methods.[25,26] The EXTEND-IA TNK study reported an advantage of the combination of tenecteplase + thrombectomy over alteplase + thrombectomy again based on perfusion neurogimaging methods.[27]

The meta-analysis of 22 studies with a total of 5623 patients studied different aspects of CTP imaging in acute ischemic stroke: IVT in patients beyond the therapeutic window, clinical outcome in patients treated with reperfusion therapies based on CTP, rate of symptomatic cerebral hemorrhages following IVT, mortality among patients after IVT based on CTP, and rate of recanalization of affected vessels following reperfusion therapies. The authors report that the CTP-based reperfusion therapies bring more benefits to the patients in the long term, this being of particular importance for mechanical thrombectomy.[28]

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A prospective study of 70 patients with ischemic stroke treated with IVT based on CTP beyond the therapeutic window (>4.5 hours) has reported that the median score on the National Institutes of Health Stroke Scale (NIHSS) is 8 points; the median 'last-known-well' time is 11.4 hours; the median score on ASPECTS is 10 points, and CTP mismatch – 90%. The patients were followed up and scored using the Modified Rankin scale (mRS). The results of the study underline the benefit and safety of CTP-based IVT performed beyond the therapeutic window.[29]

CTP-based IVT in patients with wake-up stroke (WUS) and stroke of unknown onset (SUKO)

The benefit of IVT in patients with wake-up stroke (WUS) and stroke of unknown onset (SUKO) based on CTP has been debated in recent years. Data of the studies in that aspect are limited. It is estimated that around 8%-28% of stroke patients wake up with a neurologic deficit.[30]

The WAKE-UP study included 503 patients with a stroke of unknown onset in whom diffusion-weighted imaging-fluid attenuated inversion recovery (DWI-FLAIR) was used in order to determine the duration of ischemic changes in the brain parenchyma. The study demonstrated that in the majority of cases the onset of the stroke was less than 4.5 hours making these patients good candidates for IVT.[31]

A study, which included 657 patients with acute ischemic stroke, investigated the safety and benefit of IVT (based on CTP data for penumbra) performed in a wake-up stroke, a stroke with unknown time of onset, and in patients beyond therapeutic interval (>4.5 hours from stroke onset). The patients were divided into two groups: the patients in the first group were treated within the standard therapeutic interval (n=604) and the patients in the second group were patients with a wake-up stroke, a stroke with unknown time of onset, and a stroke that occurred before more than 4.5 hours. The Modified Rankin Scale (mRS) scores of the two groups were compared at discharge and 3 months later, as well as the incidence of the complication symptomatic hemorrhage. No significant differences were found in the scores on the scales between the two groups, which proves the benefit and safety of IVT when performed based on the data from CTP, indicating presence of a large area of penumbra regardless of the stroke onset.[32]

A systematic review and a meta-analysis of 3 studies (EXTEND, ECASS4-EXTEND and EPITHET) included 414 patients over 18-years of age with ischemic stroke admitted after 4.5 hours from stroke onset or wake-up strokes with CTP performed. Of all patients, 213 (51%) were treated with alteplase and 49% (n=201) did not received thrombolytic therapy. 211 patients from the first group and 199 from the second were followed up and rated on mRS three months after the stroke. Seventy-six (36%) of the 211 patients, treated with alteplase and 58 (29%) of the 199 patients who did not receive thrombolytic therapy showed an excellent score at 3 months. The symptomatic intracerebral hemorrhages were more common in the alteplase-treated group (5% vs. 1%). Outcomes in patients treated beyond the therapeutic window based on the CTP data showed a higher mRS functional score at 3 months after the stroke.[33]

Prognostic biomarkers from CTP in the diagnosis of acute cerebral infarction

Imaging biomarkers are being increasingly used in order to acquire a better understanding of the pathophysiology and pathomorphology of various diseases, including cerebral infarction. Their use as predictors of disease outcome is still limited. A widely available, simple, and sensitive neuroimaging marker that has been established in clinical practice as a reliable prognostic factor for clinical outcome in patients with ischemic stroke is lacking. In the era of multimodal neuroimaging and, in particular, CTP, in the diagnosis of acute ischemic stroke, the search for biomarkers that are predictors of the outcome with greater applicability is required. Data from recent studies revealed that CTP with different combinations of parameters could predict the ischemic stroke outcome. CT-perfusion maps of the infarction and penumbra do correlate with DW-MRI both in the acute stage and at further follow-up.[34]

CONCLUSIONS

The critical role of neuroimaging in the fast and effective management of patients with acute ischemic stroke is incontrovertible. Indisputable is also its role in proving or excluding a hemorrhage, as well as in identifying the proximal vessel occlusion. Additional data includes assessment of the infarct core and ischemic penumbra, of collateral vessels' status, and of the risk of hemorrhagic transformation. There is no standardization regarding the CTP metrics. Selection of patients with acute ischemic stroke for conducting reperfusion therapies and predicting the clinical outcome of the disease are still challenges for clinicians. Notwithstanding this fact, CTP remains an extremely useful neuroimaging diagnostic method for ischemic stroke, which provides rapid and accurate data on the physiological state of the brain parenchyma. With the ongoing advancement of the 'penumbra' concept and the insights from scientific studies, we can increasingly affirm that 'the tissue is at least as important as time'.[35] Despite the advances in neuroimaging methods, a gold standard for precise identification of the ischemic core and penumbra is still lacking. No consensus has yet been reached on widely available and reliable imaging biomarkers with prognostic significance. Future scientific research addressing these unresolved issues would contribute to a successful scientific approach to their resolution.

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КТ-перфузия – актуальный элемент современного мультимодального диагностического подхода к острому ишемическому инсульту

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Резюме

Острый ишемический инсульт имеет большое клиническое и социальное значение в связи с его высоким процентом заболеваемости и смертности, а также тем фактом, что больные страдают от стойкой приобретённой инвалидности. Современные тенденции прямо говорят о том, что в плане диагностики заболевания должен использоваться мультидисциплинарный подход. Терапевтические шаги, которые в конечном итоге определяют клинический исход, определяются точным диагнозом острого ишемического инсульта. Узкоспециализированные учреждения для диагностики и лечения острого ишемического инсульта (инсультные отделения) работают в странах, которые вкладывают значительные средства в здравоохранение. Визуализация паренхимы головного мозга в зоне риска, или так называемой ишемической полутени, при остром ишемическом инсульте является одной из основных задач мультимодального компьютерно-томографического подхода. Наиболее быстрым методом визуализации ишемической полутени является компьютерно-томографическая перфузия (КТП). Этот метод предоставляет информацию об анатомии и физиологическом состоянии паренхимы головного мозга.

В текущем обзоре литературы представлен подробный обзор различных аспектов компьютерно-томографической перфузии при остром ишемическом инсульте и, в частности, дифференциальной диагностики острых ишемических инсультов и заболеваний, имитирующих инсульт, прогнозирования риска геморрагической трансформации, компьютерно-томографической перфузии, применяемой при внутривенном тромболизисе (IVT) за пределами терапевтического окна, инсультах пробуждения (WUS - wake-up strokes) и инсультах с неизвестным началом (SUKO), а также сообщаемых прогностических параметрах КТП в корреляции с клиническим исходом острого ишемического инсульта.

Ключевые слова

КТ-перфузия, внутривенный тромболизис, ишемический инсульт, нейровизуализация, полутень