SANAMED
2013; 8(2): 123–130
ISSN-1452-662X

UDK: 616.831-005-085.273
Originalni naučni rad

RESCUING THE ISCHEMIC PENUMBRA — OUR EXPIRIENCE

Milosavljevic Tamara,[1] Ivkovic Aleksandar[2]

[1] Special Hospital Niroshi, Nis, Serbia
[2] Center of Radiology, Klinical Center Nis, Serbia

Primljen/Received 31. 05. 2013. god.

Prihvaćen/Accepted 13. 11. 2013. god.

Abstract: **Objectives:** Over one million strokes per year are occurring in Europe. Brain stroke is one of the most important death and disability causes in Europe and USA. The main role of perfusion is to determine the border of insult core and ischemic penumbra. Penumbra can be saved with thrombolytic therapy but core have irreversible injuries and represent death of brain cells.

Aim: to determine the role of CT brain perfusion in cases of acute brain stroke and following thrombolytic therapy.

Methods: We examined 64 patients with acute brain stroke who received thrombolytic therapy after that. All patients were examining on 16 MDCT with 50 ml of iodine contrast agent following the standard procedure for CT perfusion. Patients were 34 male and 30 female with middle age of 64 years. MRI was made after thrombolytic therapy and compare with perfusion results before therapy.

Results: Using an artery and a vein as reference three parameters were measured — blood flow (CBF), blood volume (CBV) and mean transit time (MTT), for each patient. Hemorrhagic was find in 9 (14.01%) patients after thrombolytic therapy. 4 (6.25%) other patients develop new stroke of same but mostly other side of brain. 8 (12.50%) more patients finished lethally. From other 42 patients with thrombolytic therapy we can positively say that in 31 (48.44%) patients penumbra was rescued. For other 11 (17.19%) stroke was same size like firstly involved core and penumbra but not bigger.

Conclusion: CT perfusion plays major role by showing a curable parts of tissue in brain strokes.

Key worlds: penumbra, ischemia, CT perfusion, stroke.

INTRODUCTION

A stroke, or cerebrovascular accident (CVA), is the rapid loss of brain function due to disturbance in the blood supply to the brain. This can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism) or a hemorrhage (1). As a result, the affected area of the brain cannot function, which might result in an inability to move one or more limbs on one side of the body, inability to understand or formulate speech, or an inability to see one side of the visual field (2).

A stroke is a medical emergency and can cause permanent neurological damage and death. Risk factors for stroke include old age, high blood pressure, previous stroke or transient ischemic attack (TIA), diabetes, high cholesterol, tobacco smoking and atrial fibrillation (2). High blood pressure is the most important modifiable risk factor of stroke (2). It is the second leading cause of death worldwide (3). An ischemic stroke is occasionally treated in a hospital with thrombolysis (also known as a "clot buster"), and some hemorrhagic strokes benefit from neurosurgery. Treatment to recover any lost function is termed stroke rehabilitation, ideally in a stroke unit and involving health professions such as speech and language therapy, physical therapy and occupational therapy. Prevention of recurrence may involve the administration of antiplatelet drugs such as aspirin and dipyridamole, control and reduction of high blood pressure, and the use of statins. Selected patients may benefit from carotid endarterectomy and the use of anticoagulants (2). Strokes can be classified into two major categories: ischemic and hemorrhagic (4). Ischemic strokes are those that are caused by interruption of the blood supply, while hemorrhagic strokes are the ones which result from rupture of a blood vessel or an abnormal vascular structure. About 87% of strokes are caused by ischemia and the remainder by hemorrhage. Some hemorrhages develop inside areas of ischemia ("hemorrhagic transformation"). It is unknown how many hemorrhages actually start as ischemic stroke (2). In an ischemic stroke, blood supply to part of the brain is decreased, leading to dysfunc-

tion of the brain tissue in that area. There are four reasons why this might happen:

— Thrombosis (obstruction of a blood vessel by a blood clot forming locally)

— Embolism (obstruction due to an embolus from elsewhere in the body) (2)

— Systemic hypo perfusion (general decrease in blood supply, e.g., in shock) (5)

— Venous thrombosis (6).

Stroke without an obvious explanation is termed "cryptogenic" (of unknown origin); this constitutes 30–40% of all ischemic strokes (2, 7).

There are various classification systems for acute ischemic stroke. The Oxford Community Stroke Project classification (OCSP, also known as the Bamford or Oxford classification) relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI) or posterior circulation infarct (POCI). These four entities predict the extent of the stroke, the area of the brain affected, the underlying cause, and the prognosis (8, 9). The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification is based on clinical symptoms as well as results of further investigations; on this basis, a stroke is classified as being due tothrombosis or embolism due to atherosclerosis of a large artery, embolism of cardiac origin, occlusion of a small blood vessel, other determined cause, undetermined cause (two possible causes, no cause identified, or incomplete investigation) (1–5, 10).

CT perfusion is the method by which perfusion to an organ measured by CT is still a relatively new concept, although the original framework and principles were concretely laid out as early as 1980 by Leon Axel at University of California San Francisco (2). It is most commonly carried out for neuroimaging using dynamic sequential scanning of a pre-selected region of the brain during the injection of a bolus of iodinated contrast material as it travels through the vasculature (11). Various mathematical models can then be used to process the raw temporal data to ascertain quantitative information such as rate of cerebral blood flow (CBF) following an ischemic stroke or aneurismal subarachnoid hemorrhage. Practical CT perfusion as performed on modern CT scanners was first described by Ken Miles, Mike Hayball and Adrian Dixon from Cambridge UK (3) and subsequently developed by many individuals including Matthias Koenig and Ernst Klotz in Germany (4), and later by Max Wintermark in Switzerland and Ting-Yim Lee in Ontario, Canada (5).

It is important to understand the normal physiology of the brain for accurate interpretation of stroke imaging. The brain is continuously perfused with blood during systole as well as diastole, with 15–20% of the total cardiac output going to the brain. Cerebral blood flow is approximately 800 ml/min. This high and continuous blood flow is necessary as the brain uses glucose, exclusively, for energy metabolism and is unable to store energy. Cerebral blood flow is equipped with an autoregulatory mechanism, which protects against hypoxia and low perfusion. It is a multifactorial mechanism, involving neurogenic, myogenic, and metabolic controls. This autoregulation tries to maintain a mean arterial pressure of 60–100 mm Hg and a cerebral blood flow of 50–60 ml/100 gm of brain per minute. When the cerebral blood flow decreases, the autoregulatory mechanism tries to compensate by increasing the blood pressure and inducing vasodilatation. However, if the blood flow decreases so much that it falls below a critical level, infarction results (Table 1).

Table 1. *Cerebral perfusion and corresponding blood flow levels*

Brain perfusion	Cerebral blood flow
Normal	> 50–60 ml/100 gm/min
Oligemic	30–60 ml/100 gm/min
Ischemic	20–30 ml/100 gm/min
Infarction	< 10 ml/100 gm/min

Stroke imaging serves two purposes: first, to diagnose or confirm the occurrence of a stroke and, second, to assess the amount of potentially salvageable brain tissue and irreversibly infarcted tissue; both are necessary, the first for planning management strategy and the second for prognostication. CT perfusion (CTP) is a tool that has been successfully employed to assess the extent of salvageable tissue. It is most commonly carried out for neuroimaging using dynamic sequential scanning of a pre-selected region of the brain during the injection of a bolus of iodinated contrast material as it travels through the vasculature. Various mathematical models can then be used to process the raw temporal data to ascertain quantitative information such as rate of cerebral blood flow (CBF) following an ischemic stroke.

AIM

The aim of this retrospective study is to show possibilities of CT perfusion as diagnostic procedure in patients with acute ischemic attack.

METHODS

We retrospectivly reviewed examination of 64 patients with acute brain stroke who have received thrombolytic therapy after that. All patients were examined

from January 2010 to October 2012. The research included 34 (53.13%) male and 30 (46.87%) female, with average age of the patients 57.42188 ± 5.31 years, range 45–74 years. All patients were examined on GE Bright Speed 16 MDCT with 50 ml of iodine contrast agent (Ultravist 300, Bayer) following the standard procedure for CT perfusion. All examinations were made in period of 4 hours after the first symptom. After CT perfusion, we performed Multi Raw Detector Computer Tomography Angiography (MDCTA) of brain. MDCTA was performed using standard GE protocol for brain blood vessels, using 60 to 120 ml of iodine contrast agent (Ultravist 370). Results were presented using ASPECTS (Alberta Stroke Program Early CT Score) and using NIHSS (National Institute of Health Stroke Scale) by neurologist. Patients were treated using Tissue plasminogen activator (rtPA) in dose of 0.9 mg/kg body weight, by Guidance for ischemic stroke, 10% in bolus injection and rest of dose during 60 minutes intravenous. Magnetic Resonance Imaging (MRI) was made on Siemens Avanto 1.5T MRI, using standard Siemens protocol with apparent diffusion coefficients (ADC) map and diffusion weighted images (DWI) after thrombolytic therapy and compared with perfusion results before therapy. Using the General Electric Neuro software, CBV was calculated along with cerebral blood flow, using the maximal slope model, which has been shown to yield lesion volumes that are similar to delay insensitive deconvolution techniques. The hypoperfused areas on CBV maps were defined as volume abnormality. The infarct core was outlined on CBV maps as a severely hypoperfused area displayed by 2 colors in the color bar. The CBV threshold was defined at 2.0 mL 100 g1. Each CBV map was analyzed by demarcating trace lines around the area of volume abnormality on each of the 4 slices by hand-drawn regions of interest. The area of volume abnormality was defined as CBV area. The weighted mean of CBV and CBV area was calculated in each of the 4 slices, respectively, and used for statistical analysis. For statistical analysis we used means with standard deviation and variance, also population standard deviance and variance were used. Present-day multislice CTs do not allow for whole-brain perfusion assessment. Thus, if an anterior circulation infarct is suspected, data acquisition is done at the basal ganglia level and if a posterior circulation infarct is likely, then at it is done at the level of the mid-cerebellum. Depending upon the type of scanner, one can take 1–4 sections of 5–10 mm thickness at the levels mentioned.

Postprocessing of the data is done by using specialized software. It involves confirmation of certain parameters which are automatically chosen by the software, and it generates color perfusion maps as well as time–attenuation curves (TAC) from which T-TP/MTT, CBV, and CBF can be calculated for any area of interest.

RESULTS

All patients were examined in short time period of 4 hours after initial symptoms (Figure 1). Patients were examined by neurologist before sending to MDCT examination. Patients meeting neurology standards for thrombolytic therapy were transferred to MDCT. First we performed non-contrast CT (Figure 2). All patients were scored by ASPECTS (Alberta Stroke Program Early CT Score). Patients with score 6 or above were expected for good candidate for thrombolytic therapy (Figure 3). Pa-

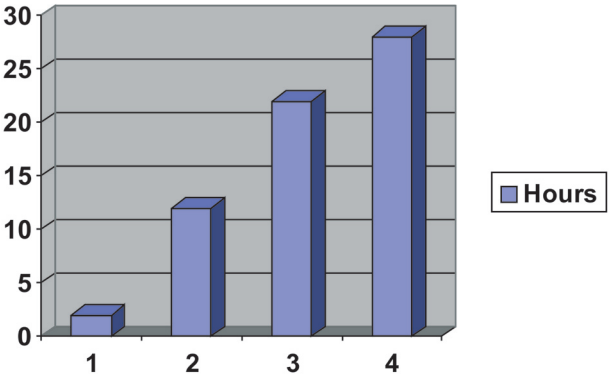

Figure 1. *Number of patients according to hours of stroke*

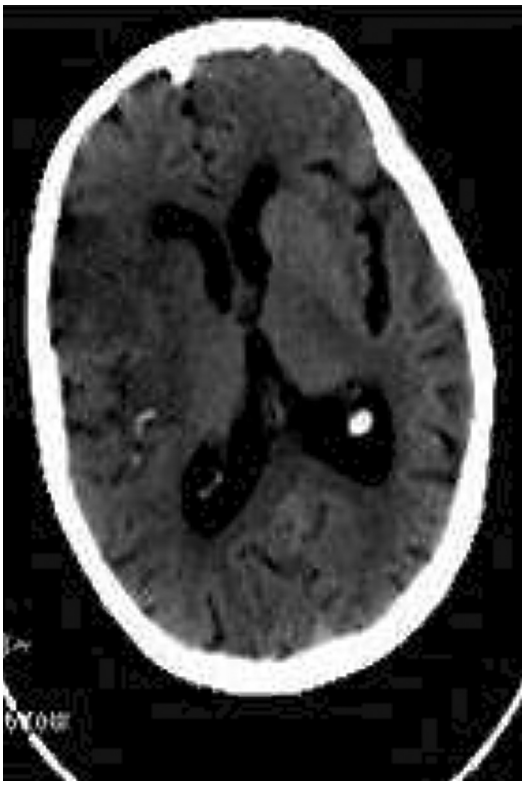

Figure 2. *Noncontrast computed tomography with CVI of right temporal lobe*

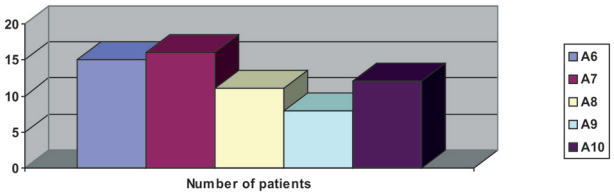

Figure 3. *Number of patients according to ASPECTS*

tients with score below 6 were not used in consideration for therapy. Average number of patients were 12.8 with standard deviation of 3.114 and variance of 9.7. Population standard deviation were 2.786 with variance of 7.76. After NCCT we performed perfusion MDCT. Main area of interest was middle cerebral artery (MCA), using an artery and a vein as reference. Three parameters were measured — blood flow (CBF), blood volume (CBV) and mean transit time (MTT), for each patient. Also we performed white/grey separation program to determine borders of white and gray matter (Figure 4).

Hemorrhagic insult was found in 9 (14.01%) patients after thrombolytic therapy. Presents of intracerebral hemorrhage is the most feared risk of intravenous use of tissue plasminogen activator (rtPA). According to ASPECTS, 4 were with ASPECTS 6, another 4 with ASPECTS 7 and 1 with ASPECTS 8 (Figure 5).

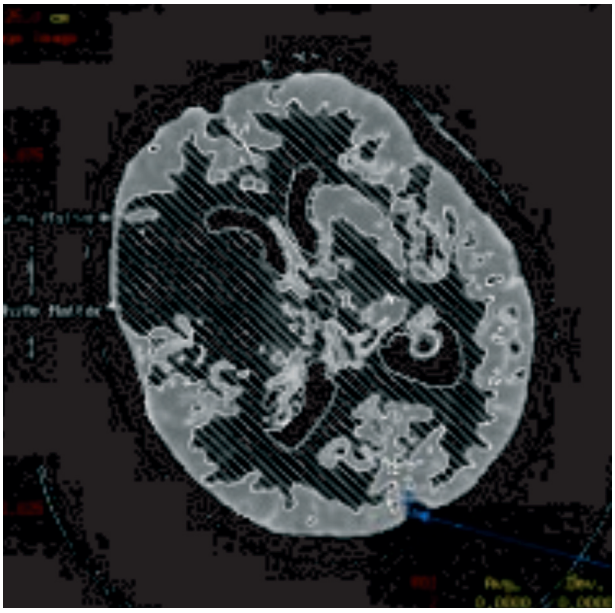

Figure 4. *White/grey mater differentiation*

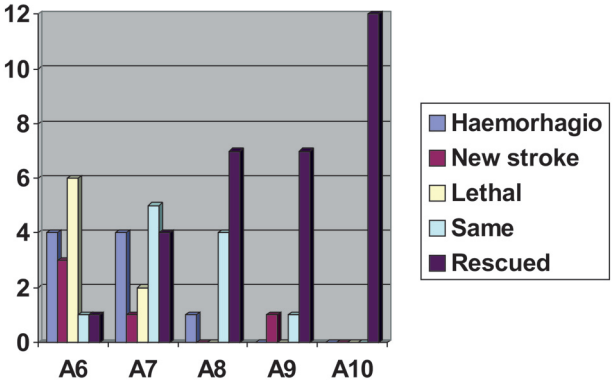

Figure 5. *Distribution of patients according to ASPECTS*

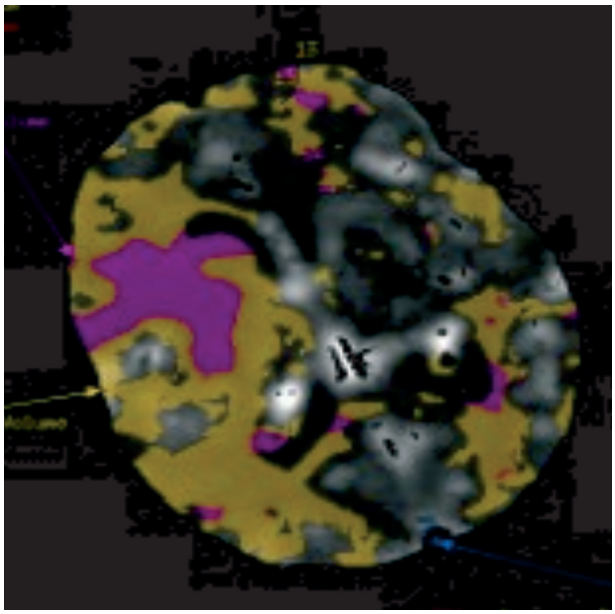

Figure 6. *CT perfusion. CVI of right temporal lobe*

Four (7.81%) other patients develop new stroke of same, but mostly other side of brain. According to ASPECTS, 3 were with ASPECTS 6, another 1 with ASPECTS 7 (Figure 5).

Eight (12.50%) more patients finished lethally (Figure 6. and 7). According to ASPECTS, 6 were with ASPECTS 6, another 2 with ASPECTS 7 (Figure 5).

For other 11 (17.19%) patients stroke was same size like involved core and penumbra on first examination but not bigger. Patients with ASPECTS score below 8 and patients on upper time window are more likely to

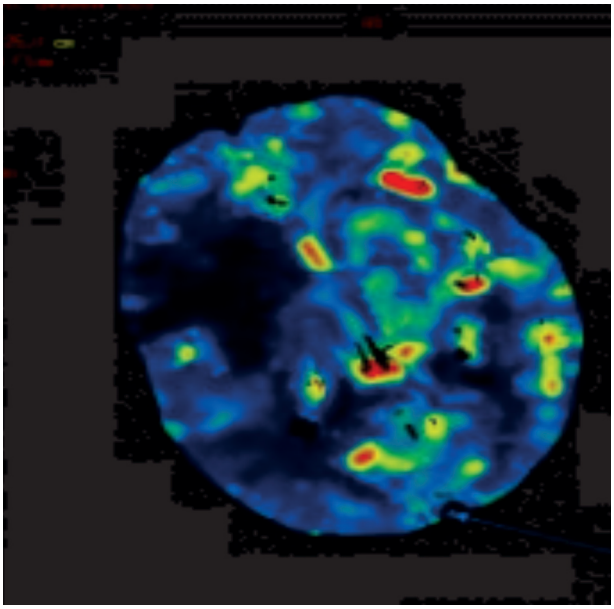

Figure 7. *CT perfusion. CVI of right temporal lobe*

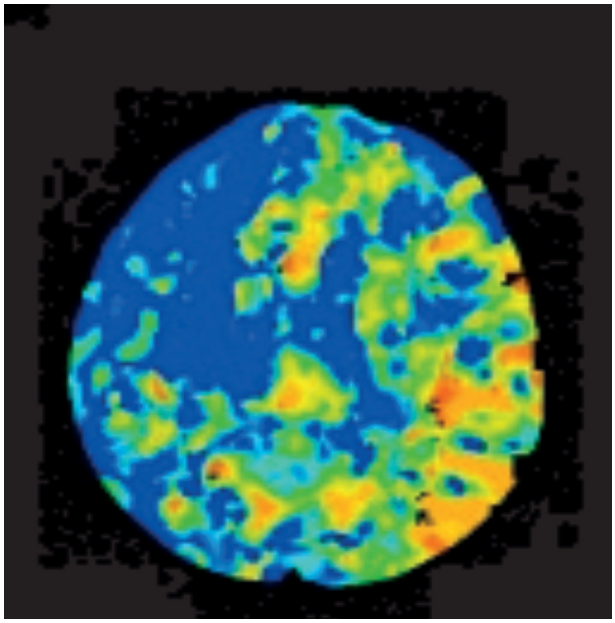

Figure 8. *CT perfusion of massive CVI without penumbra*

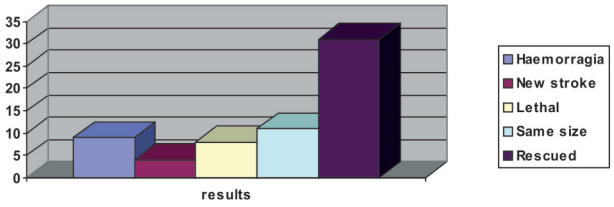

Figure 9. *Number of patients according to results*

be in this group: 1 patient was with ASPECTS 6, another 5 patients were with ASPECTS score 7, another 4 with ASPECTS 8 and 4 in time window after 4 hours of stroke (Figure 8). Only one was with ASPECTS 9 and treated in first 4 hour (Figure 5).

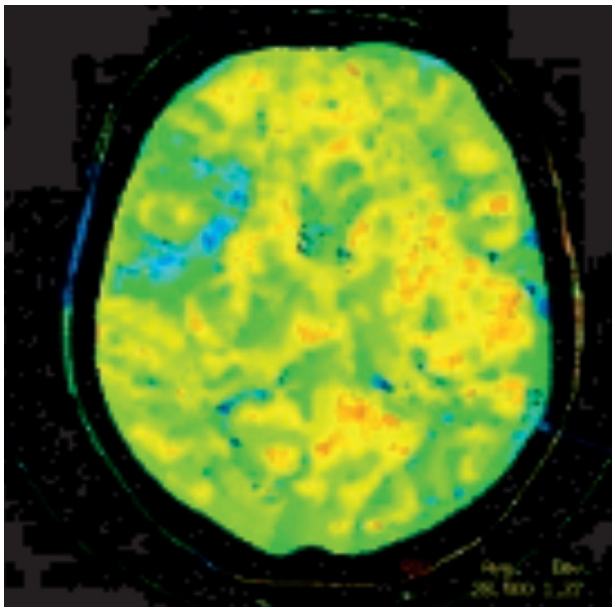

Figure 10. *CT perfusion after thrombolitic therapy with rescued penumbra*

We can positively say that in 31 (48.44%) patients penumbra was rescued. Penumbra can not be saved without therapy so we can positively say that penumbra was saved in 48.44% of patients with high ASPECTS and treated in first 4 hours (Figure 9). However, the rescued penumbra may be affected by selective neuronal loss. Rescuing penumbra is more likely in first 3 hours after the stroke, with no mater of penumbra size (Figure 10). ASPECTS were 10 in 12 patients, 9 in 8 patients, 8 in 7 patients, 7 in 4 patients and 6 in 1 patient (Figure 5).

DISCUSSION

Ischemic stroke occurs because of a loss of blood supply to part of the brain, initiating the ischemic cascade (12). Brain tissue ceases to function if deprived of oxygen for more than 60 to 90 seconds, and after approximately three hours will suffer irreversible injury possibly leading to death of the tissue, i.e., infarction (13). (This is why fibrinolytics such as alteplase are given only until four hours since the onset of the stroke.) Atherosclerosis may disrupt the blood supply by narrowing the lumen of blood vessels leading to a reduction of blood flow, by causing the formation of blood clots within the vessel, or by releasing showers of small emboli through the disintegration of atherosclerotic plaques. Since blood vessels in the brain are now occluded, the brain becomes low in energy, and thus it resorts into using anaerobic metabolism within the region of brain tissue affected by ischemia. Unfortunately, this kind of metabolism produces less adenosine triphosphate (ATP) but releases a by-product called lactic acid. Lactic acid is an irritant which could potentially destroy cells since it is an acid and disrupts the normal acid-base balance in the brain. The ischemia area is referred to as the “ischemic penumbra”.

In our study hemorrhagic insult after thrombolytic therapy occurred in 14.01% of patients. According to Berger et al. the 7-level mRS predictive model indicates that 32% of patients who experienced intracerebral hemorrhage were destined for a fatal outcome even they had not been treated with rtPA (12). According to National Institute of Neurological Disorders and Stroke, hemorrhagic insult will occur in 7 to 33% of patients depending of age, sex, recurrent stroke and ASPECTS (4). Our percent of 14.01 is tempered and balanced with ASPECTS.

New stroke occurred in 7.81% of patients. According to literature, percentage of new stroke is from 4% to 32% and mostly is depending on heart condition and patient’s age (12, 13, 14). We have had low percentage of these patients because of high ASPECTS.

Lethal result was in 12.50% of patients. According to literature patients finish lethal in 10 to 28%. Accord-

ing to Quareshi et al. “the problem of disentangling worsening attributable to cerebral edema, infarct expansion, and other causes of ischemic stroke progression from worsening attributable to hemorrhage is difficult because the variables that independently identify patients destined for thrombolysis are also variables that predict symptomatic worsening and poor final outcome even if patients are not treated with rtPA” (13).

Same size of penumbra occurred in 17.19% of patients. According to Nor et al., same size of penumbra occurs in 15 to 25% of patients, depending on time of initial stroke (15).

In 48.44% of patients penumbra was rescued. According to O’Sullivan et al, penumbra can be rescued in less than half of patients and according to Fisher, percentage of rescued penumbra is 42 to 49% (16, 17).

CT angiography (CTA) is an advanced application of present-day multislice spiral CT scan machines. It allows the comprehensive evaluation of arteries anywhere in the body. This is useful in the assessment of stenosis or occlusion of the carotid arteries or vertebral arteries in the neck, which can act as predisposing factors for a stroke. Also, the evaluation of intracranial arteries is possible with a high degree of accuracy (18). CTA is now gradually replacing digital subtraction angiography (DSA) for this purpose.

MR imaging has become a powerful clinical tool for evaluation of brain anatomy. Its application has recently expanded into evaluation of brain function via assessment of a number of functional or metabolic parameters. One such parameter is cerebral perfusion, which describes passage of blood through the brain’s vascular network. MRI diffusion as on Figure 11 (MRI diffusion after stroke) and perfusion as on Figure 12.

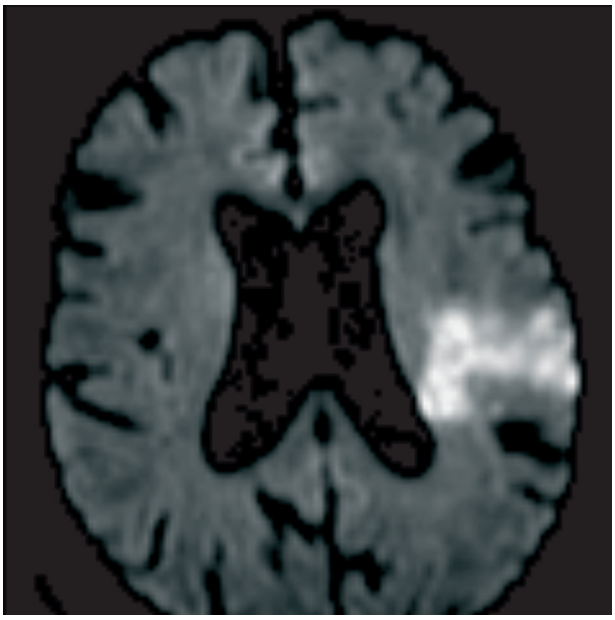

Figure 11. *MRI diffusion of CVI*

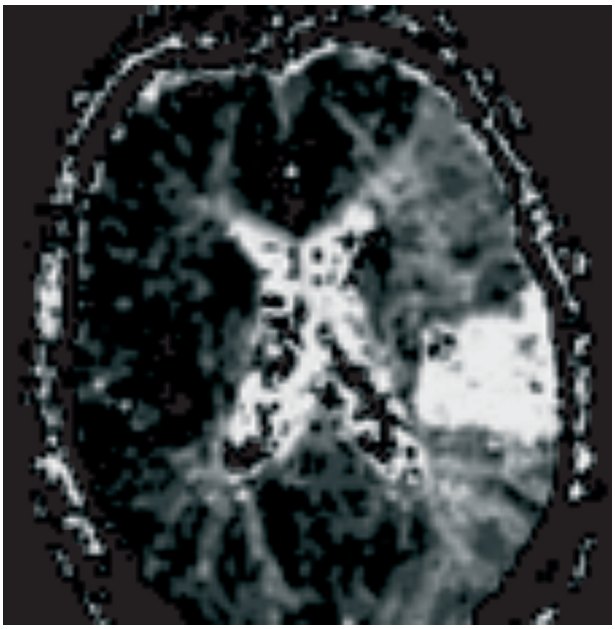

Figure 12. *MRI perfusion of CVI*

(MRI perfusion after stroke) imaging provide similar information with greater sensitivity and specificity. Probably the widest application of exogenous tracer methods in MR perfusion imaging has been in the assessment of cerebral ischemia.

CONCLUSION

The American Heart Association has provided certain guidelines and recommendations for imaging of cerebral ischemia. According to it, quantitative CTP may probably be useful to differentiate between reversible and irreversible ischemic tissue in acute stroke. On the other hand, MRI perfusion and diffusion techniques are probably useful in differentiating between reversible and irreversible ischemic tissue in acute stroke patients. According to our results, CTP is a valuable and important tool in stroke imaging and we perform MRI mostly after thrombolytic therapy. High percentage of rescued penumbra is most important result because there is no other diagnostic tool but must be performed on selective patients and in first 4 hours.

List of abbreviations

CBF — cerebral blood flow
CBV — cerebral blood volume
MTT — mean transit time
CVA — cerebro vascular incident
TIA — transient ischemic attack
TACI — total anterior circulation infarct
PACI — parcial anterior circulation infarct
LACI — lacunar infarct
POCI — posterior circulation infarct

CTP — CT perfusion
ASPECTS — Alberta Stroke Program Early CT Score
rtPA — tissue plasminogen activator
ADC — apparent diffusion coefficients
DWI — diffusion weighted images
TAC — time-attenuation curves
MCA — middle cerebral artery
ATP — adenosine triphosphate
DSA — digital supstaction angiography

Sažetak

SPASAVANJE ISHEMIJSKE PENUMBRE — NAŠA ISKUSTVA

Milosavljević Tamara,[1] Ivković Aleksandar[2]

[1] Specijalna Internistička bolnica Niroshi, Niš, Srbija
[2] Centar za radiologiju, Klinički Centar Niš, Srbija

Uvod: Preko milion moždanih udara se dogodi u Evropi godišnje. Moždani udar predstavlja jedan od najvažnijih uzroka smrti kako u Evropi tako i u SAD. Glavna uloga CT perfuzije je da odredi granicu penumbre i jezgra insulta. Jezgro je pretrpelo ireverzibilne promene dok penumbra može biti spašena. Jezgro će kasnijim procesom biti izloženo nekrozi, što sledi i penumbri ukoliko nema trombolitičke terapije.

Cilj: odrediti ulogu CT moždane perfuzije u slučajevima akutnog moždanog udara i praćenje efekata trombolitičke terapije.

Metodi: Perfusion measurements of the brain: using dynamic CT for the quantitative assessment of cerebral ischemia in acute stroke Pregledano je ukupno 64 pacijenta sa akutnim moždanim udarom, koji su primili trombolitičku terapiju nakon toga. Svi pacijenti su pregledani na 16 MSCT aparatu uz upotrebu 50 ml jodnog kontrastnog sredstva po standardnom protokolu za CT perfuziju. MRI je rađen nakon trombolitičke terapije i upoređivani su nalazi sa perfuzijom pre terapije.

Rezultati: Koristeći vene i arterije kao repere vršena su tri merenja — protok krvi (blood flow-CBF), volumen krvi (blood volume-CBV) i srednje vreme tranzicije (mean transit time-MTT), i to za svakog pacijenta. U našoj studiji se trudimo da odredimo i granicu bele i sive mase radi jasnije neurološke prognoze. Hemoragija je nađena kod 9 (14.01%) pacijenata nakon trombolitičke terapije. Četiri (6.25%) pacijenta su imala reinzult, na istoj ili suprotnoj strani, što je bilo češće. Osam (12.50%) pacijenata je završilo letalno. Od ostalih 42 pacijenata možemo sa sigurnošću reći da je penumbra spašena kod 31 (48.44%). Kod ostalih 11 (17.19%) insult je bio jednak jezgru i penumbri ali ne veći.

Zaključak: CT perfuzija ima značajnu ulogu u prikazivanju delova mozga podložnih lečenju.

Ključne reči: penumbra, ishemija, CT perfuzija, insult.

REFERENCES

1. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochimica et Biophysica Acta. 2009; 1802 (1): 80–91.

2. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008; 371(2): 1612–23.

3. Mathers, CD, Boerma T, Ma Fat D. Global and regional causes of death. British medical bulletin. 2009; 92: 7–32.

4. Klotz E, König M. Perfusion measurements of the brain: using dynamic CT for the quantitative assessment of cerebral ischemia in acute stroke. Eur J Radiol. 1999 Jun; 30(3): 170–84.

5. Shuaib A, Hachinski VC. Mechanisms and management of stroke in the elderly. CMAJ . 1998; 145 (5): 433–43.

6. Stam J. Thrombosis of the cerebral veins and sinuses. The New England Journal of Medicine. 352 (17): 1791–8.

7. Guercini F, Acciarresi M, Agnelli G, Paciaroni M. Cryptogenic stroke: time to determine aetiology. Journal of Thrombosis and Haemostasis. 2008; 6 (4): 549–54.

8. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991; 337 (8756): 1521–6.

9. Bamford JM. The role of the clinical examination in the subclassification of stroke. Cerebrovascular Diseases. 2001; 10 Suppl 4: 2–4.

10. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Stroke. 1998; 24 (1): 35–41.

11. Goldstein LB, Simel DL. Is this patient having a stroke? JAMA. 2005; 293 (19): 2391–402.

12. Berger C, Fiorelli M, Steiner T, Schabitz WR, Bozzao L, Bluhmki E, Hacke W, von Kummer R. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? Stroke. 2001; 32: 1330–5.

13. Qureshi AI, Suarez JI, Yahia AM, Mohammad Y, Uzun G, Suri MF, Zaidat OO, Ayata C, Ali Z, Wityk RJ. Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. Crit Care Med. 2003; 31: 272–7.

14. Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S. Design and retrospective analysis of the Los Angeles Prehospital Stroke Screen (LAPSS). Prehospital Emergency Care. 2005; 2 (4): 267–73.

15. Nor AM, Davis J, Sen B, et al. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development

and validation of a stroke recognition instrument. Lancet Neurology. 2005; 4 (11): 727–34.

16. O'Sullivan, Susan. B. Stroke. In: O'Sullivan, SB, Schmitz TJ, editors. Physical Rehabilitation 5. Philadelphia: FA Davis Company; 2008. p. 719.

17. Fisher. The arterial lesions underlying lacunes. Acta Neuropathologica. 1998; 12 (1): 1–15.

18. Milosavljevic T, Ivkovic A. Rescuing of ishemic penumbra. The good and the bed side of CT perfusion. Proceedings of 7th Europian Congress of Radiology; 2011 Mar 3–7: Vienna.

Correspondence to/Autor za korespondenciju
Tamara Milosavljević,
Specijalna Internistička bolnica Niroshi, Niš
Romanijska 7/18, 18000 Niš,
tamaradr2009@gmail.com
060 7000 182, fax 018 520 174