

Successful outcome after endovascular thrombolysis for acute ischemic stroke with basis on perfusion-diffusion mismatch after 24 h of symptoms onset

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Abstract

Background: Although intravenous thrombolysis is the Food and Drug Administration-approved treatment for acute ischemic stroke (AIS) within 3 h, combined intravenous and intra-arterial thrombolysis with endovascular techniques may be able to extend this traditional time window.

Case Description: We present the clinical evolution of a 45-year-old male presenting with acute left hemiparesis. Magnetic resonance imaging revealed a small diffusion restriction at the right basal ganglia with perfusion compromise in the entire right middle cerebral artery (MCA) territory. Angiography revealed a complete occlusion of MCA at its M1 segment. The patient underwent endovascular mechanical thrombectomy with additional intra-arterial thrombolysis more than 24 hours after the onset of the initial symptoms and experienced complete vessel recanalization. At 1 year, the patient had global independence with minor residual motor impairment in the left arm.

Conclusions: We report the case of a successful thrombolytic therapy following AIS performed more than 24 h after the initial symptoms based on the presence of a perfusion-diffusion mismatch. This report is expected to stimulate the development of future prospective studies with special focus on the role of perfusion-diffusion mismatch in patient selection for treatment of AIS, especially in those presenting outside the traditional time window.

Key Words: Acute ischemic stroke, intra-arterial thrombolysis, mechanical thrombectomy, perfusion-diffusion mismatch, thrombolysis

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INTRODUCTION

Administration of recombinant tissue plasminogen activator (rt-PA/alteplase) is currently approved by the US Food and Drug Administration for intravenous (IV) use in the treatment of acute ischemic stroke (AIS) only within 3 h after the onset of symptoms.^[28] Nevertheless, even with continued improvement in the

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efficiency of both emergency medical services and intra-hospital care for acute ischemic stroke, due to such a strict timeframe, only a small proportion of patients with AIS presenting to Emergency Departments are eligible for standard IV thrombolytic therapy.^[18] In fact, it has been estimated that only 3–10% of those patients possibly eligible for IV rt-PA therapy actually end up receiving the drug.^[4]

According to an observational study from the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry, the time window for IV rt-PA treatment can be safely extended from 3 h to 4.5 h after stroke onset with no difference in the outcome measures between both timeframes.^[31] Furthermore, it has already been shown that beyond 3 h of symptoms onset (and perhaps even within 3 h), patient selection seems to be the most critical variable associated with improved outcomes.^[17] In addition to clinical factors, the most important imaging criteria for indicating thrombolytic therapy that has emerged in the last decade is the concept of perfusion-diffusion (PWI/DWI) mismatch, an imaging modality which is able to provide an accurate measure of the cerebral tissue at risk of bioenergetic failure.^[7]

Regarding the available methods of thrombolysis, several protocols of rt-PA administration (such as intra-arterial thrombolysis, combined IV and intra-arterial salvage thrombolysis) as well as endovascular techniques (such as mechanical thrombolysis with or without angioplasty) have been proposed as alternatives to IV thrombolysis for patients presenting with significant PWI/DWI mismatch and outside of the classic 3-h window.^[5,11,25,28] In the vast majority of such protocols, the presence of PWI/DWI mismatch has been used as definitive criteria for indication of thrombolysis.^[2]

An institutional protocol was recently adopted in our stroke center with the purpose of implementing endovascular mechanical thrombolysis followed by low doses of intra-arterial thrombolytic therapy (4U of rt-PA plus incremental doses of IU via super-selective catheterization) as a salvage therapy for patients with AIS presenting after 3 h from symptoms onset and in whom the magnetic resonance imaging (MRI) demonstrates a significant PWI/DWI mismatch.

In this case report, we present a patient with AIS from a right middle cerebral artery (MCA) occlusion who was submitted to salvage therapy with mechanical thrombolysis and intra-arterial rt-PA more than 24 h after the onset of initial symptoms on the basis of PWI/DWI mismatch. In the sequence, we discuss recent advances in stroke imaging relevant to such a case with particular attention to the concept of ischemic penumbra and the MRI PWI/DWI mismatch model.

CASE DESCRIPTION

A 45-year-old male presented to the Emergency Department with an acute episode of central left facial palsy (House–Brackmann Grade III and National Institutes of Health Stroke Scale of 9) 10 h after the symptoms onset. No other abnormalities were identified on the initial neurological exam. The MRI performed at the Emergency Department demonstrated diffusion restriction on the right globus pallidus and head of the caudate nucleus. There was no PWI/DWI mismatch at that time [Figure 1a and b]. Twelve hours later, the patient presented with progressive worsening of the symptoms, becoming hemiplegic on the left side. The new MRI (performed approximately 22 h after the first symptoms) revealed no major extension of the diffusion restriction but did reveal significant compromise of the perfusion in the whole territory of the right MCA [Figure 1c], with an estimated PWI/DWI mismatch >60%. MR angiography reconstructions suggested acute occlusion of the right MCA at the M1 segment [Figure 1d and e].

The case was presented to the endovascular team which decided to submit the patient to a digital subtraction angiography which confirmed complete occlusion of the proximal MCA [Figure 2a]. At that point, more than 24 h had already passed from the initial symptoms onset. Given the patient's young age, the absence of major clinical

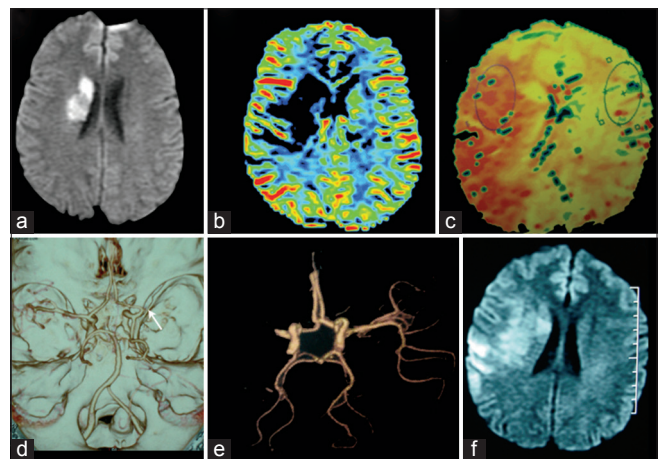


Figure 1: (a and b) Magnetic resonance imaging performed 12 h after initial symptoms revealing diffusion-weighted imaging-restriction at the right basal ganglia with perfusion compromise only in this area. No significant perfusion-diffusion mismatch was identified. (c) Perfusion-weighted imaging performed after neurologic decline 22 h after the initial symptoms demonstrating increased perfusion-weighted imaging compromise affecting the entire right middle cerebral artery territory. (d and e) Magnetic resonance angiography suggesting an acute thrombus in right middle cerebral artery (M1 segment). (f) Follow-up magnetic resonance imaging 12 months after the stroke demonstrating the final infarct area, which includes the basal ganglia area which initially presented the diffusion restriction plus an additional cortical region, likely representing a borderline-zone of perfusion

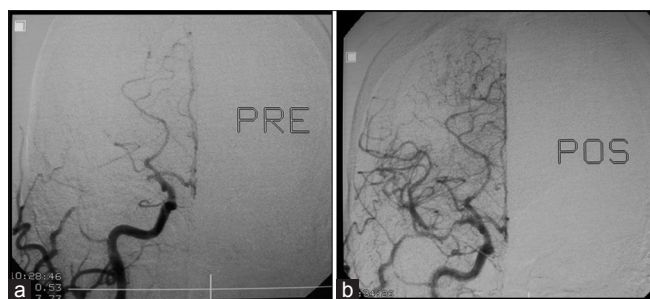


Figure 2: Digital subtraction angiography images demonstrating an acute occlusion of the right middle cerebral artery at its M1 portion (a) as well as successful recanalization after mechanical thrombolysis with additional intra-arterial thrombolysis (b)

morbidities, and the fact that the new MRI demonstrated a significant PWI/DWI mismatch, an interventional approach was considered. After an extensive discussion with the family about the risks and benefits of such procedure, the endovascular team decided to perform a combined mechanical thrombolysis followed by intra-arterial thrombolysis. A microcatheter was advanced until the superior trunk of the right M1, and the thrombus was removed with a clot retrieval system (Catch mechanical thrombectomy device, Balt, Montmorency/France). After the mechanical thrombolysis, rt-PA was injected super-selectively in the right M1 at an initial dose of 4U followed by two additional doses of 1U until the digital subtraction angiography demonstrated complete recanalization of the MCA [Figure 2b].

After the interventional procedure, the patient was transferred to the Intensive Care Unit. A control angiography performed 7 days later confirmed the sustained recanalization of the right MCA, with the presence of some residual stenosis [Figure 3a and b]. It was also possible to observe the absence of flow in the capillary phase at the area of initial diffusion-weighted imaging (DWI)-restriction that had progressed to infarction [Figure 3c and d - arrows]. The endovascular team discussed with the patient and the family the option of intracranial angioplasty for the residual M1 stenosis. However, as the patient was progressively improving, they decided to pursue a conservative approach. After 10 days of in-hospital care, the patient was discharged to a rehabilitation facility with complete left-arm paralysis and left central facial palsy. At the 11-month clinical follow-up, the patient had improved strength in the left superior limb (proximal strength Grade IV and distal Grade II) whereas the left facial paresis had completely resolved. By that time, he was considered to have a modified Rankin scale of 2 and a Barthel index of 85.

According to the family, the patient currently has an independent life with minor restrictions for his daily activities, especially regarding activities demanding fine movements with the left hand. The MRI performed 12 months after the procedure demonstrated the final

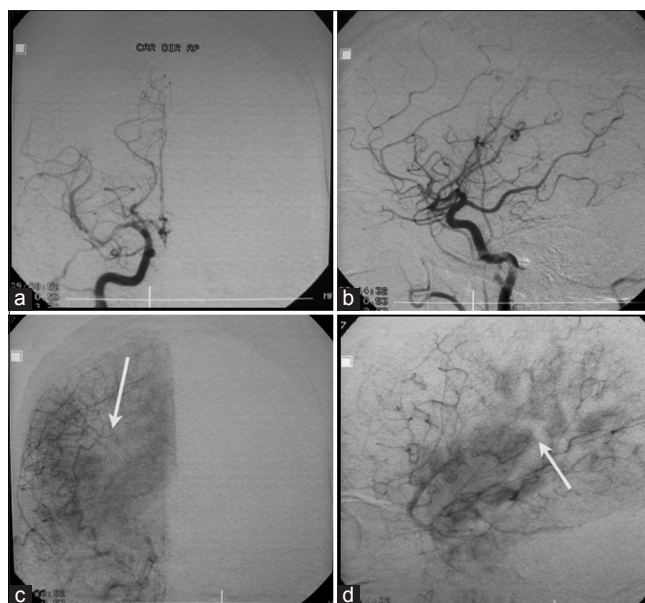


Figure 3: Control digital subtraction angiography performed 7 days after the thrombolysis confirming the sustained recanalization of the right middle cerebral artery (a: Anteroposterior and b: Lateral views) as well as the absence of flow in the capillary phase (arrows) at the area of diffusion-weighted imaging-restriction that progressed to infarction (c: Anteroposterior and d: Lateral)

infarction area (as revealed by the fluid-attenuated inversion recovery [FLAIR] sequence) consisting of the initial area of diffusion restriction before the thrombolysis with an additional cortical zone which likely represented an area of borderline perfusion [Figure 1e].

DISCUSSION

Imaging in acute ischemic stroke

Imaging has become one of the main cornerstones of AIS management. Due to its availability, computed tomography (CT-scan) still remains the standard imaging modality for initial assessment of patients arriving within 3 h of symptom onset in most of centers around the world.^[32] However, several studies have shown that MRI-based thrombolysis protocols demonstrate an improved safety profile as well as greater efficacy than standard CT-based ones, irrespective of the time window.^[10,17] Additionally, recent studies have demonstrated that MRI may be as accurate as CT-scan in the detection of hyperacute intraparenchymal hemorrhage in patients with acute focal stroke symptoms (and may be even more accurate than CT for the detection of chronic intracerebral hemorrhage), supporting the role of MRI as a suitable sole imaging modality for initial evaluation of AIS.^[15,16] Some groups have reported successful outcomes of endovascular revascularization in patients with AIS with a protocol based solely in CT, CT-angiogram, and CT perfusion scans as means of evaluation of the possible salvageable brain tissue.^[3,22] However, it is questionable if

such protocols would be noninferior to those employing MRI PWI/DWI mismatch. Actually, the fact that the above-mentioned series,^[22] which focused on patients presenting beyond 8 h from symptoms onset, reported a relatively high incidence of perioperative mortality (23.3%) and high long-term morbidity rates (with a very high mean modified Rankin scale at last follow-up of 4.2) and, suggests that the employed radiological criteria may have been too broad, including patients which, ultimately, may not have benefited from the aggressive intervention.

Diffusion-perfusion mismatch

In the last decades, DWI and perfusion-weighted imaging (PWI) MRI techniques have significantly expanded the role of MRI in the initial evaluation of patients with AIS. In simple terms, by quantifying the isotropic diffusivity of water (a putative measure of intracellular edema), DWI sequences can determine the areas under significant bioenergetic compromise during AIS. On the other hand, PWI, a functional imaging method which is able to provide a comparative assessment of the changes in blood flow between both hemispheres, provides additional information on the regional measures of hemodynamic impairment, enabling an indirect inference of local metabolism. Combining the data from these two imaging modalities, it is possible not only to delineate the area under acute ischemic compromise but also to identify those regions under high-risk of ischemic injury due to impaired cerebral blood flow.^[23]

The concept of PWI/DWI mismatch, which arose from early studies on multimodal MRI for AIS, has proven to be an important diagnostic tool as it is able to provide a simple and feasible means for identification of the so-called “ischemic penumbra.”^[24,26,29] According to this model, the diffusion abnormality represents the core of ischemia, an area of cerebral tissue which has suffered, at least theoretically, irreversible ischemic changes, while the outer rim of the visualized perfusion abnormality defines the area under abnormal blood flow. The region with perfusion abnormality but no diffusion changes, the so-called “perfusion/diffusion” mismatch, represents the area of penumbra. This region represents an area of brain tissue that is hypoperfused but has not yet experienced advanced bioenergetic failure and, therefore, at least in theory, may still be salvageable.^[9]

It is important to emphasize that the PWI/DWI mismatch has been successfully used in the literature as an accurate surrogate marker of penumbra and ischemic core not only in the presence of total proximal arterial obstruction but also in cases of partial arterial obstructions and oscillating neurological symptoms.^[19] In the reported case, both the insidious clinical presentation (with the patient presenting only a mild initial facial paresis with sudden onset of hemiplegia 12 h later), as well as the radiological evidence from the obtained

angiograms [Figure 2] (which demonstrate some evidence of collateral circulation from the external carotid artery as well as the presence of a residual MCA stenosis after thrombolysis), suggest that the most likely scenario was a partial occlusion of the right MCA leading to a small area of infarct, ultimately progressing to a complete MCA occlusion.

It has already been demonstrated that most patients presenting with AIS have an area of penumbra (PWI/DWI mismatch) within the first 6 h from symptoms onset.^[27] After this period, the penumbra area tends to progress either to irreversible infarct or to complete restoration of its normal function. It has also been demonstrated that the presence of PWI/DWI mismatch, or penumbra, is commonly, but not invariably, associated with proximal arterial occlusion and it is time-dependent.^[30]

Although such initial concepts of core infarct, penumbra area, and perfusion compromise region have significantly improved the understanding of the pathophysiology of AIS, there is sufficient data to support a possible major paradigm shift in some classic concepts regarding the DWI/PWI mismatch model.^[6] It has already been shown, for example, that the PWI/DWI mismatch does not optimally define the penumbra area. In fact, the visible zone of perfusion abnormality seems to overestimate the penumbra by including regions of “benign oligemia.” Similarly, it has already been demonstrated that a small portion of the abnormal-DWI region may be potentially salvageable with rapid reperfusion and, therefore, represents an area of penumbra and not part of the ischemic core.^[14] In relation to the different perfusion techniques, as we have already discussed in another opportunity,^[20] recent studies have suggested that cerebral blood volume, but not time-to-peak maps, significantly correlate with infarct growth, representing the true area of penumbra.^[12,21] It is important to emphasize that although PWI/DWI mismatch is usually more pronounced in the first 6 h, it has already been shown that a significant PWI/DWI mismatch may be present up to 24 h from the initial symptoms onset.^[8,19] Darby *et al.* for example, demonstrated that while the presence and volume of mismatch progressively decrease over time, approximately 60–70% of patients will still have substantial regions of mismatch up to 24 h after the initial symptoms.^[8] These findings are supported by a previous study employing positron emission tomography which demonstrated the presence of a penumbra area in AIS up to 48 h after the initial symptoms onset.^[19]

Based on such data, several authors have suggested that, in selected patients, the time window available for reperfusion of the penumbra area may be much longer than the traditional 3 or 6 h.^[1,13] In such cases, it has been shown that the PWI/DWI mismatch is one of the most important criteria which enables the proper identification

of that subgroup of patients which may benefit from additional salvage thrombolytic therapies.

In the presented case, for example, the PWI/DWI mismatch was very sensitive in identifying the penumbra area, which was successfully reperfused (compare the DWI restriction [Figure 1a] with the final area of infarct at the late follow-up MRI [Figure 1f]). The FLAIR sequence of the MRI obtained 1 year after the thrombolysis demonstrates that the final infarct area includes the initial area of DWI compromise [Figure 1a] plus an additional cortical area, which probably represented a borderline zone of perfusion that eventually progressed to infarct.

CONCLUSIONS

Several trials have already demonstrated that mechanical thrombolysis (with or without intra-arterial rt-PA infusion) may be a safe and efficacious salvage therapy for treatment of AIS due to proximal arterial occlusion in patients presenting outside of the classic 3 h time window for IV thrombolysis.

In this report, we present the case of a successful thrombolytic therapy in a patient with AIS due to proximal arterial occlusion performed more than 24 h after the initial symptoms. Although the anecdotal evidence provided by this case report does not support the overall safety and efficacy of mechanical thrombolysis outside the standard 3 or 6 h window, it is expected to stimulate the development of future prospective studies with special focus on the role of PWI/DWI mismatch in patient selection for treatment of AIS, as well as the possible associated nuances of such imaging tool (such as the use of perfusion maps based on time-to-peak or on cerebral blood volume, for example). Ultimately, due to the significant heterogeneity regarding the initial presentation and evolution of AIS patients, future trials may find more useful to employ objective measures of ischemic core and penumbra areas (such as MRI PWI/DWI mismatch), instead of basing the decision-making exclusively on the time from initial symptoms.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. *Stroke* 2010;41:1996-2000.
- Ahn JY, Han IB, Chung SS, Chung YS, Kim SH, Yoon PH. Endovascular thrombolysis and stenting of a middle cerebral artery occlusion beyond 6 hours post-attack: Special reference to the usefulness of diffusion-perfusion MRI. *Neurol Res* 2006;28:881-5.
- Amenta PS, Ali MS, Dumont AS, Gonzalez LF, Tjoumakaris SI, Hasan D, et al. Computed tomography perfusion-based selection of patients for endovascular recanalization. *Neurosurg Focus* 2011;30:E6.
- Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology* 2001;56:1015-20.
- Brekenfeld C, Schroth G, Mattle HP, Do DD, Remonda L, Mordasini P, et al. Stent placement in acute cerebral artery occlusion: Use of a self-expandable intracranial stent for acute stroke treatment. *Stroke* 2009;40:847-52.
- Butcher KS, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C, et al. Refining the perfusion-diffusion mismatch hypothesis. *Stroke* 2005;36:1153-9.
- Chen F, Ni YC. Magnetic resonance diffusion-perfusion mismatch in acute ischemic stroke: An update. *World J Radiol* 2012;4:63-74.
- Darby DG, Barber PA, Gerraty RP, Desmond PM, Yang Q, Parsons M, et al. Pathophysiological topography of acute ischemia by combined diffusion-weighted and perfusion MRI. *Stroke* 1999;30:2043-52.
- Davis SM, Donnan GA, Butcher KS, Parsons M. Selection of thrombolytic therapy beyond 3 h using magnetic resonance imaging. *Curr Opin Neurol* 2005;18:47-52.
- de Lucas EM, Sánchez E, Gutiérrez A, Mandly AG, Ruiz E, Flórez AF, et al. CT protocol for acute stroke: Tips and tricks for general radiologists. *Radiographics* 2008;28:1673-87.
- Flaherty ML, Woo D, Kissela B, Jauch E, Pancioli A, Carrozella J, et al. Combined IV and intra-arterial thrombolysis for acute ischemic stroke. *Neurology* 2005;64:386-8.
- Hong CT, Sun Y, Lu CJ, Shin HC, Chen RC. Prediction of infarct growth and neurologic deterioration in patients with positive perfusion-diffusion mismatch. *Clin Neurol Neurosurg* 2012;114:376-80.
- Jovin TG, Liebeskind DS, Gupta R, Rhymer M, Rai A, Zaidat OO, et al. Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: Retrospective multicenter analysis of 237 consecutive patients. *Stroke* 2011;42:2206-11.
- Kidwell CS, Alger JR, Saver JL. Beyond mismatch: Evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging. *Stroke* 2003;34:2729-35.
- Kidwell CS, Chalea JA, Saver JL, Davis SM, Warach S. Hemorrhage early MRI evaluation (HEME) study: Preliminary results of a multicenter trial of neuroimaging in patients with acute stroke symptoms within 6 hours of onset. *Stroke* 2003;34:239.
- Kidwell CS, Chalea JA, Saver JL, Starkman S, Hill MD, Demchuk AM, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA* 2004;292:1823-30.
- Köhrmann M, Jüttler E, Fiebich JB, Huttner HB, Siebert S, Schwark C, et al. MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: A cohort study. *Lancet Neurol* 2006;5:661-7.
- Lahr MM, Luijckx GJ, Vroomen PC, van der Zee DJ, Buskens E. The chain of care enabling tPA treatment in acute ischemic stroke: A comprehensive review of organisational models. *J Neurol* 2013;260:960-8.
- Lee VH, John S, Mohammad Y, Prabhakaran S. Computed tomography perfusion imaging in spectacular shrinking deficit. *J Stroke Cerebrovasc Dis* 2012;21:94-101.
- Marchal G, Beaudouin V, Rioux P, de la Sayette V, Le Doze F, Viader F, et al. Prolonged persistence of substantial volumes of potentially viable brain tissue after stroke: A correlative PET-CT study with voxel-based data analysis. *Stroke* 1996;27:599-606.
- Mattei TA. Extending thrombolytic therapy beyond 6 h: Which 'mismatch' are you talking about? *Clin Neurol Neurosurg* 2012;114:1205-6.
- Natarajan SK, Snyder KV, Siddiqui AH, Ionita CC, Hopkins LN, Levy EI. Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes. *Stroke* 2009;40:3269-74.
- Nentwich LM, Veloz W. Neuroimaging in acute stroke. *Emerg Med Clin North Am* 2012;30:659-80.
- Neumann-Haefelin T, Wittsack HJ, Wenserski F, Siebler M, Seitz RJ, Mödder U, et al. Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke. *Stroke* 1999;30:1591-7.
- Qureshi AI, Siddiqui AM, Suri MF, Kim SH, Ali Z, Yahia AM, et al. Aggressive mechanical clot disruption and low-dose intra-arterial third-generation thrombolytic agent for ischemic stroke: A prospective study. *Neurosurgery* 2002;51:1319-27.
- Rordorf G, Koroshetz WJ, Copen WA, Cramer SC, Schaefer PW,

- Budzick RF Jr., et al. Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI. *Stroke* 1998;29:939-43.
27. Schellinger PD, Fiebich JB, Jansen O, Ringleb PA, Mohr A, Steiner T, et al. Stroke magnetic resonance imaging within 6 hours after onset of hyperacute cerebral ischemia. *Ann Neurol* 2001;49:460-9.
28. Syfret DA, Mitchell P, Dowling R, Yan B. Does intra-arterial thrombolysis have a role as first-line intervention in acute ischaemic stroke? *Intern Med J* 2011;41:220-6.
29. Thomalla GJ, Kucinski T, Schoder V, Fiehler J, Knab R, Zeumer H, et al. Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. *Stroke* 2003;34:1892-9.
30. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995;333:1581-7.
31. Wahlgren N, Ahmed N, Dávalos A, Hacke W, Millán M, Muir K, et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): An observational study. *Lancet* 2008;372:1303-9.
32. Wintermark M, Sincic R, Sridhar D, Chien JD. Cerebral perfusion CT: Technique and clinical applications. *J Neuroradiol* 2008;35:253-60.