Multimodal CT imaging in ischemic stroke

Wijngaard, I.R. van den

CHAPTER 1

General introduction and outline

INTRODUCTION

Background

Stroke is one of the leading causes of mortality and disability worldwide.(1;2) Over the last decades, the absolute number of people with first stroke has increased and this number is expected to rise in the coming years.(3) In the Netherlands about 46.000 people suffer a stroke per year, while this number is approximately 17 million worldwide. (3;4)

Strokes can be classified into two major categories: ischemic and hemorrhagic. Differentiating between these different types of stroke at presentation is important because management differs. In the Western world the proportion of stroke due to ischemia is almost 90%.(5;6) Ischemic strokes result from a reduction or complete blockage of blood flow. About 80% of acute ischemic strokes (AIS) involve the anterior (i.e. carotid territory) circulation, and 20% involve the posterior (i.e. vertebrobasilar territory) circulation.(7;8) Neuroimaging plays a vital role in the workup of acute stroke patients providing information important for diagnosis, etiology, prognosis and treatment.

Current reperfusion therapies in the acute stage of ischemic stroke are: (1) intravenous thrombolysis (IVT) with recombinant tissue type plasminogen activator (IV-rtPA) within the first 4.5 hours after symptom onset, and (2) intra-arterial therapy (IAT) within the first 6 hours after onset, which refers to endovascular catheter-based clot removal.(9) IAT is only indicated in patients with a documented proximal intracranial arterial occlusion which accounts for approximately one third of acute ischemic stroke cases.(10)

Clinical presentation and stroke severity

The presentation of patients with acute ischemic stroke (AIS) ranges from minor isolated symptoms to devastating deficits. The National Institutes of Health Stroke Scale (NIHSS) is a widely used clinical measure of stroke severity and is a strong independent predictor of patient outcome.(11) The NIHSS measures neurologic impairment with an 11-item scale, and has a range of 0 to 42, with higher scores indicating more severe neurologic deficits. Multiple population-based samplings of ischemic stroke cases show that the majority of strokes are in the 0-10 NIHSS range.(12;13) The NIHSS score is associated with the likelihood of large artery occlusion (i.e. possible candidates for IAT). The positive predictive value of an NIHSS score of ≥9 is 86% to find an occluded artery on CT-angiography or MR-angiography.(14)

Infarct core and penumbra

Most ischemic strokes are caused by an occlusion of a blood vessel and its downstream branches. Most affected is the region directly surrounding the occluded vessel. Cells in a central core tissue will be damaged irreversibly and die by necrosis if the duration of ischemia is too long. Other cells may receive a small amount of oxygen and glucose from collateral vessels. The region of salvageable tissue (if blood flow is promptly restored) is called the penumbra. (15;16)

"Time is Brain"-paradigm and acute ischemic stroke treatment

Each minute in which a large vessel ischemic stroke is untreated, the average patient loses about 2 million neurons, 14 billion synapses and 12 km of axonal fibers.(17) Revascularization therapies in acute ischemic stroke patients, including intravenous thrombolysis (IVT) and intra-arterial treatment (IAT), aim to rescue the ischemic penumbra by restoring the patency of the occluded artery (recanalization) and the downstream capillary blood flow (reperfusion). The benefit of AIS treatment decreases continuously over time from symptom-onset. Earlier treatment is associated with larger benefits for both IVT(18;19) and IAT.(20) For example, a recent meta-analysis showed that in patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with less functional independence (absolute risk reduction of 5.2%).(21)

Imaging in acute ischemic stroke

Neuroimaging of the cerebrovascular status and hemodynamics has vastly improved our understanding of stroke mechanisms and provided information for therapeutic decision-making and improved prognostication.(22) Various kinds of imaging techniques have been established for these purposes including computed tomography (CT) techniques, magnetic resonance imaging (MRI) techniques and digital subtraction angiography (DSA). Each modality has particular advantages and limitations.(22)

The invasive nature, complication risk and expertise requirements, have limited the routine use of DSA in AIS patients. Although MRI is a non-invasive modality, it has shortcomings such as contraindications, time-consumption, limited 24/7 availability and relatively higher costs. As a technique with fast acquisition, relatively low costs, acceptable tolerance and a 24/7 availability, CT has become the most widely used modality for the acute stroke setting. Great efforts have been made towards improving the CT techniques in the last years.(22;23) Currently, the most commonly used tool for acute ischemic stroke in clinical practice is multimodal CT which combines non-contrast CT (NCCT), CT angiography (CTA) with or without CT perfusion (CTP). NCCT allows distinction of hemorrhagic stroke from ischemic stroke, while it also provides an indication of the extent of ischemic changes. To evaluate the extent of early ischemic changes, the Alberta Stroke Program Early CT (ASPECT) score is most commonly used.(24) CTA can identify the presence and extent of arterial occlusion and assess the collateral status. CTP provides hemodynamic information on a tissue-based level and can be used to estimate infarct core and penumbra volume.

CT angiography acquisition

Acquisition of CTA can be performed in various ways; all methods entail obtaining raw imaging data by scanning patients after intravenous administration of an iodinated contrast agent (Figure 1) The difference between methods is based on the scanning mode: static (also known as single-phase), multi-static (i.e. multi-phase) and dynamic mode.

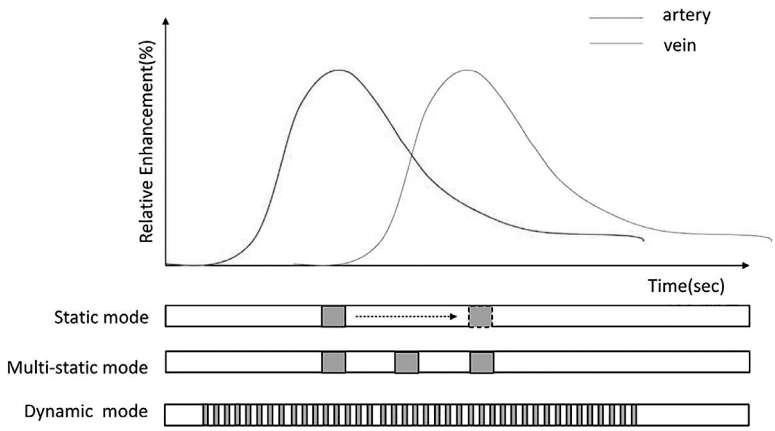

Figure 1: Relative contrast enhancement to time curve and image acquisition modes. Each voxel in the scanned brain volume is enhanced with contrast dynamically which is depicted by a relative contrast enhancement-time curve. In static or single-phase mode, the acquisition is performed at a single time point after contrast injection. In ischemic stroke, single-phase CTA is focused on the proximal cerebral arteries where occlusive lesions commonly occur, whereas modifications of this approach can also be used to focus on venous structures in the application of CT-venography. The multi-static (i.e. multi-phase) mode is basically repeating static mode acquisition for more than one time at different time points during a single contrast injection (3 time-points are shown in this figure). Dynamic mode is serial scanning over time of the targeted slice.

Dynamic mode: CT perfusion/4D-CTA

Dynamic, time-resolved or 4D-CTA is a technique that combines the noninvasive nature of CTA with the dynamic acquisition of DSA. It enables the noninvasive evaluation of flow dynamics of the intracranial vasculature by multiple subsequent CT acquisitions or a continuous volume CT acquisition for a period of time.(25)

The principle of dynamic mode is to monitor the process of contrast bolus passing through the cerebrovasculature and adjacent brain tissue.(22) The acquisition is supposed to scan the targeted region of brain repeatedly after contrast injection (Figure 1). Since CT perfusion was the first application of this approach, data of this acquisition mode are often referred to as 'CT perfusion/4D-CTA', which are time-resolved images of each scanned slice. Furthermore, the time–density curve of each scanned voxel can be generated with the acquired data. A major shortcoming of initial techniques was limited coverage in the craniocaudal direction depending on scanner detector width, which is only 4 cm with 64-slice multidetector CT scanners. Further development of CT scanners by increasing the detector size to 256-row or even 320-row allows whole-brain coverage. With the extending coverage, especially when advanced CT scanners also provide thinner slice scanning, detailed hemodynamic data of the whole brain as well as vasculature became available.(22;25)

Depending on the required temporal resolution discontinuously or continuously dynamic acquisitions can be performed.(25) For example, the detection of abnormal early filling

of venous structures (in an arterial venous fistula) requires a high temporal resolution of 4D-CTA. The trade-off is a higher radiation dose for patients. When collateral flow in case of an arterial occlusion needs to be evaluated, a lower temporal resolution will probably be sufficient.(25) For example, in our whole-brain CT perfusion/4D-CTA studies we scanned 19 volumes during one minute.

Clinical application of dynamic volume CT in ischemic stroke: collaterals, tissue perfusion and venous drainage

Collaterals in acute ischemic stroke

The cerebral collateral circulation is a network of blood vessels designed to preserve cerebral blood flow when primary routes fail.(26) Collaterals play an important role in pathophysiology of ischemic stroke by providing complementary blood supply into the territory of the occluded or stenotic artery. Multiple studies have shown that collateral status has a strong relationship with clinical outcome for acute ischemic stroke patients receiving IVT (27) and IAT.(28) The ability to predict clinical outcome based on assessment of pial arterial filling is better with multiphase CTA (Figure 2) than with single-phase CTA.(29) Detailed analysis of dynamic CTA in AIS (Figure 3) and implications of collateral assessment on outcome is lacking.

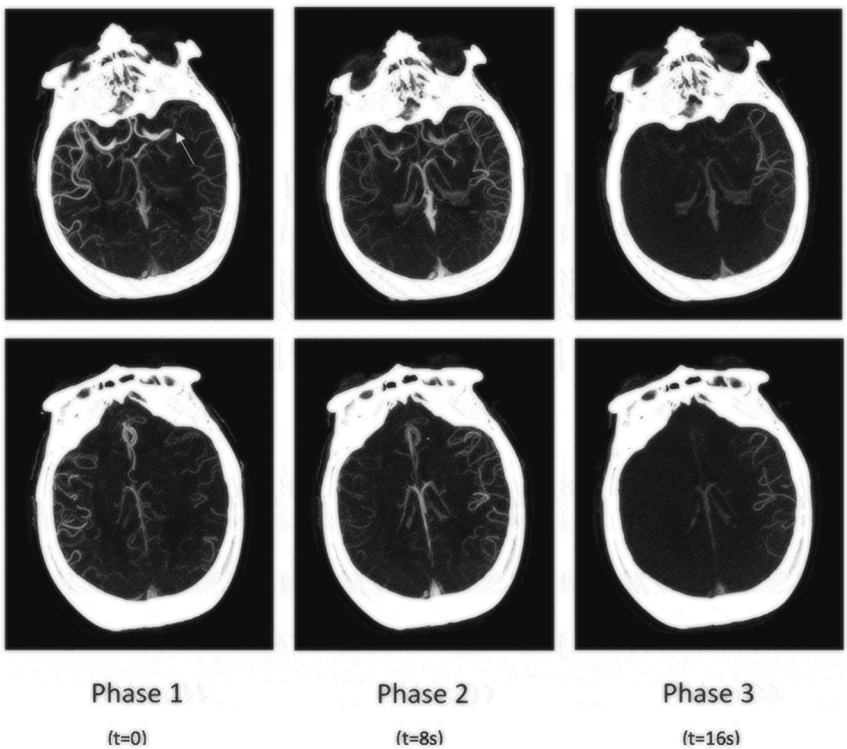

Figure 2: An example of multiphase CT angiography. Maximum intensity projection (MIP) images are shown (two levels). The patient has left middle cerebral artery (MCA) occlusion (arrow). Pial arterial filling is modest, with a delay of one phase when compared with the contralateral side.

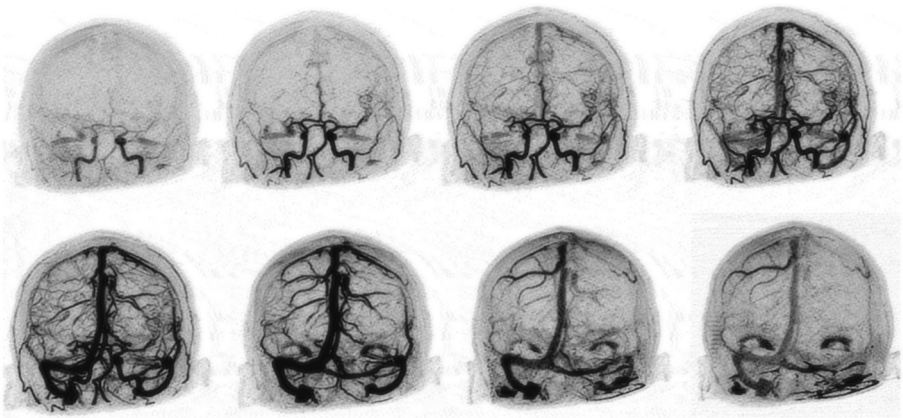

Figure 3: An example of dynamic CT angiography. Maximum intensity projection (MIP) images in coronal plane of 8 (of total 19) time points are shown. The cerebral vessels can be viewed to fill in with contrast dynamically over time. The upper left image depicts the first time point (early arterial phase), whereas the lower right image depicts the last time point (late venous phase). In the example above, a middle cerebral artery (M1 segment) occlusion at the right side is shown with delayed venous outflow of the right hemisphere.

CT perfusion

Computed tomography perfusion (CTP) can be used to estimate regions of irreversible brain damage and potentially salvageable regions with hypoperfusion.(30) The physiological data derived from CTP are typically displayed in perfusion maps, including cerebral blood flow (CBF), cerebral blood volume (CBV), time-to-peak (TTP) and mean transit time (MTT) (Figure 4). Regions of brain with severely reduced CBV or CBF correspond to the region of core infarction.(31) Regions of brain with prolongation of the MTT, TTP and time-to-maximum (Tmax) of the residue function, have been used to estimate the penumbra in patients with acute ischemic stroke.(31) CTP increases the sensitivity and specificity of the acute ischemic stroke diagnosis and aids in excluding stroke mimics.(31)

Information on stroke tissue pathophysiology has been shown to predict infarct volume.(32) However, CTP did not have additional value for the prediction of clinical outcome in a large study.(33) Some studies suggest that CTP can assist in decision making for IVT(34) and IAT.(35) At this moment, however, the use of CTP to guide selection of patients for stroke treatment is controversial because of several limitations of CTP.(36;37) Most problematic remains the significant variability in CTP technique between different institutions and CT scanners, moreover CTP parameters used to define infarct core and penumbra vary by the postprocessing software and prior institutional optimization.(31)

Another issue is that z-axis coverage of CTP studies are often limited to 40-60mm on most CT scanners currently used in clinical practice; this limited coverage leads to underestimation of the ischemic lesion.(38) Newer multi-detector CT scanners can be used to overcome this spatial limitation because they provide whole brain coverage.(39) (Figure 5)

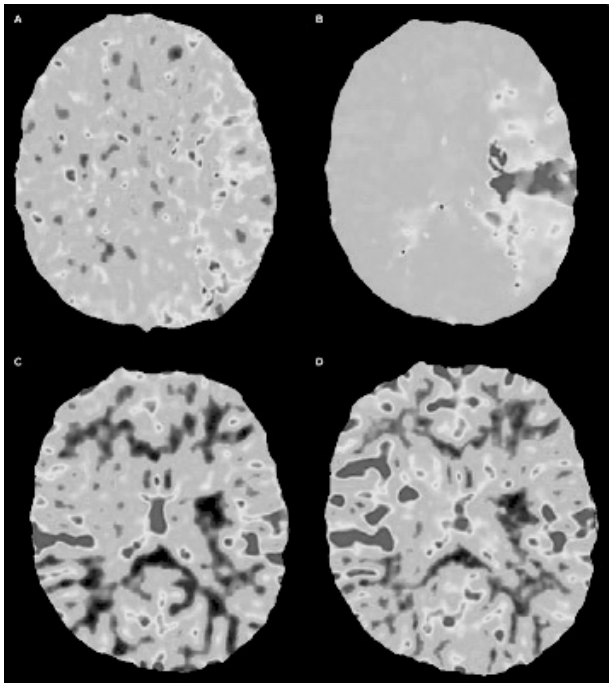

Figure 4: CT perfusion map. Axial CT perfusion shows an extensive area of the left middle cerebral artery territory with increased mean transit time (A) and time-to-peak (B), while only a limited area shows a decreased cerebral blood volume (C) and flow (D), suggesting a favourable penumbral pattern.

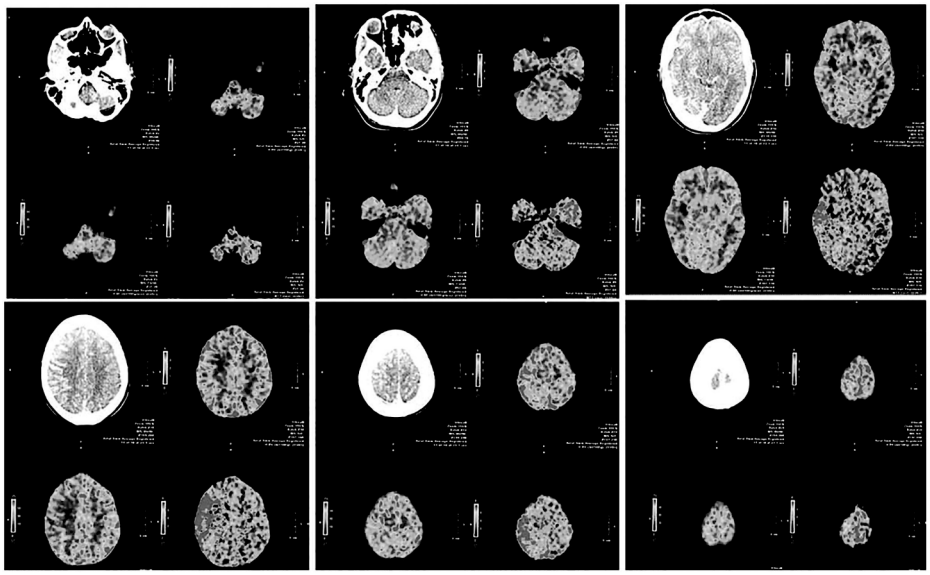

Figure 5: An example of whole brain CT perfusion. The coverage is from the skull base to vertex (6 levels are shown). The upper left image depicts the most caudal level, whereas the lower right image depicts the most cranial level.

Venous outflow in acute ischemic stroke

Poor cortical venous filling in the downstream territory of an occluded artery is a promising prognostic feature, which may be defined by the extent of collaterals and resultant perfusion.(40) Measuring the extent and velocity of venous filling with time-resolved CTA has not been studied before and data on the prognostic value and its potential role in treatment selection are lacking.

Prognosis

The primary clinical outcome measure in many neurovascular trials is the score on the modified Rankin scale at 3 months follow-up. The modified Rankin scale is a 7-point disability scale ranging from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.(41) Traditionally, models of clinical outcome after AIS have reported amongst others patient age, stroke severity, extent of early ischemic changes on non-contrast-CT and time from symptom-onset to IVT and IAT as independent predictors of clinical outcome.(19;24;42) Currently the decision to initiate acute stroke treatment depends largely on a generalized statistical rule regarding time to presentation rather than on an individualized pathophysiologic assessment of the ischemic brain tissue (at risk).(32) With the advent of modern neuro-imaging techniques and recent advances of endovascular stroke treatment, a new era has started in which an individualized pathophysiologic assessment of the ischemic brain could potentially improve (the prediction of) patient outcome.

OUTLINE OF THIS THESIS

Part I Collateral circulation in anterior circulation ischemic stroke

In the first part of this thesis we focus on the collateral circulation in acute anterior circulation ischemic stroke. **Chapter 2** provides methodological aspects of collateral assessment with dynamic CT-angiography (CTA). We compare the assessment of the collateral circulation with dynamic CTA and single-phase CTA in ischemic stroke patients. We describe the relationship between the collateral status at presentation and infarct volume at follow-up imaging. In **Chapter 3**, we focus on the association between collateral status, as assessed with dynamic CTA, and clinical outcome.

Part II Whole Brain Computed Tomography Perfusion in TIA and ischemic stroke patients

In the second part we assess the value of CT perfusion for predicting clinical outcome in TIA and ischemic stroke patients. First, in **Chapter 4**, we focus on transient ischemic attack and minor ischemic stroke patients and the value of qualitative assessment of whole brain CT perfusion for predicting outcome. We describe the prognostic value of whole brain CT perfusion in addition to known clinical and radiological predictors of clinical outcome. In **Chapter 5**, we explore the value of quantitative whole brain CT perfusion assessment for predicting outcome. With different perfusion analysis methods and multiple coverage sizes, we explore in this chapter the value of quantitative CTP assessment for predicting infarct volume at follow-up and functional outcome.

Part III Imaging features and the value of endovascular therapy in (a) childhood stroke and (b) intracranial atherosclerotic stenosis

In **Chapter 6** we present a case report and provide a short overview of acute stroke treatment in children. In **Chapter 7** we give an extensive overview of important diagnostic features and therapeutic options in patients with ischemia due to intracranial atherosclerotic stenosis. Whereas the focus of the other chapters is on the emergency setting, chapter 7 addresses imaging in the subacute phase in combination with secondary stroke prevention.

Part IV Cortical venous outflow in patients with anterior circulation stroke

In **Chapter 8** we describe a novel predictor of outcome: the value of cortical venous filling (CVF) assessed with dynamic CTA in acute ischemic stroke patients. In our new era of effective endovascular stroke therapy, we also address the interaction between CVF and treatment. We explore the influence of good CVF status at presentation on dynamic CTA in combination with good reperfusion status after endovascular treatment, on clinical outcome.

Finally, in **Chapter 9**, we discuss the research presented in this thesis and its implications for clinical practice and future research.

REFERENCE LIST

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.
2. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-223.
3. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383:245-54.
4. https://www.hartstichting.nl/hart-vaten/cijfers/beroerte Accessed September 28th, 2016
5. Kleindorfer DO, Khoury J, Moomaw CJ, Alwell K, Woo D, Flaherty ML, et al. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. Stroke 2010 ;41:1326-31.
6. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016;133:e38-e360.
7. Michel P, Odier C, Rutgers M, Reichhart M, Maeder P, Meuli R, et al. The Acute STroke Registry and Analysis of Lausanne (ASTRAL): design and baseline analysis of an ischemic stroke registry including acute multimodal imaging. Stroke 2010;41:2491-8.
8. Bornstein NM, Aronovich BD, Karepov VG, Gur AY, Treves TA, Oved M, et al. The Tel Aviv Stroke Registry. 3600 consecutive patients. Stroke 1996;27:1770-3.
9. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46:3020-35.
10. Hansen CK, Christensen A, Ovesen C, Havsteen I, Christensen H. Stroke severity and incidence of acute large vessel occlusions in patients with hyper-acute cerebral ischemia: results from a prospective cohort study based on CT-angiography (CTA). Int J Stroke 2015;10:336-42.
11. Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126-31.
12. Reeves M, Khoury J, Alwell K, Moomaw C, Flaherty M, Woo D, et al. Distribution of National Institutes of Health stroke scale in the Cincinnati/Northern Kentucky Stroke Study. Stroke 2013;44:3211-3.
13. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, et al. Long-term functional recovery after first ischemic stroke: the Northern Manhattan Study. Stroke 2009 ;40:2805-11.
14. Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono ML, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. Stroke 2013;44:1153-7.

15. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology 2010;17:197-218.

16. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke 2006;37:979-85.

17. Saver JL. Time is brain--quantified. Stroke 2006;37:263-6.

18. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695-703.

19. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-35.

20. Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, et al. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol 2016;73:190-6.

21. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. JAMA 2016;316:1279-88.

22. Jia B, Scalzo F, Agbayani E, Woolf GW, Liu L, Miao Z, et al. Multimodal CT techniques for cerebrovascular and hemodynamic evaluation of ischemic stroke: occlusion, collaterals, and perfusion. Expert Rev Neurother 2016;16:515-25.

23. Snyder KV, Mokin M, Bates VE. Neurologic applications of whole-brain volumetric multidetector computed tomography. Neurol Clin 2014;32:237-51.

24. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355:1670-4.

25. Kortman HG, Smit EJ, Oei MT, Manniesing R, Prokop M, Meijer FJ. 4D-CTA in neurovascular disease: a review. AJNR Am J Neuroradiol 2015;36:1026-33.

26. Sheth SA, Liebeskind DS. Imaging Evaluation of Collaterals in the Brain: Physiology and Clinical Translation. Curr Radiol Rep 2014;2:29.

27. Rusanen H, Saarinen JT, Sillanpaa N. Collateral Circulation Predicts the Size of the Infarct Core and the Proportion of Salvageable Penumbra in Hyperacute Ischemic Stroke Patients Treated with Intravenous Thrombolysis. Cerebrovasc Dis 2015;40:182-90.

28. Leng X, Fang H, Leung TW, Mao C, Miao Z, Liu L, et al. Impact of collaterals on the efficacy and safety of endovascular treatment in acute ischaemic stroke: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2016;87:537-44.

29. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. Radiology 2015;275:510-20.

30. Murphy BD, Fox AJ, Lee DH, Sahlas DJ, Black SE, Hogan MJ, et al. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. Stroke 2006;37:1771-7.

31. Heit JJ, Wintermark M. Perfusion Computed Tomography for the Evaluation of Acute Ischemic Stroke: Strengths and Pitfalls. Stroke 2016;47:1153-8.

32. van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, et al. CT angiography and CT perfusion improve prediction of infarct volume in patients with anterior circulation stroke. Neuroradiology 2016;58:327-37.

33. van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, et al. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc Dis 2015;40:258-69.

34. Bivard A, Levi C, Krishnamurthy V, McElduff P, Miteff F, Spratt NJ, et al. Perfusion computed tomography to assist decision making for stroke thrombolysis. Brain 2015;138:1919-31.

35. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009-18.

36. Borst J, Berkhemer OA, Roos YB, van Bavel E, van Zwam WH, van Oostenbrugge RJ, et al. Value of Computed Tomographic Perfusion-Based Patient Selection for Intra-Arterial Acute Ischemic Stroke Treatment. Stroke 2015;46:3375-82.

37. Boned S, Padroni M, Rubiera M, Tomasello A, Coscojuela P, Romero N, et al. Admission CT perfusion may overestimate initial infarct core: the ghost infarct core concept. J Neurointerv Surg 2016, Epub ahead of print.

38. Page M, Nandurkar D, Crossett MP, Stuckey SL, Lau KP, Kenning N, et al. Comparison of 4 cm Z-axis and 16 cm Z-axis multidetector CT perfusion. Eur Radiol 2010;20:1508-14.

39. Lin L, Bivard A, Krishnamurthy V, Levi CR, Parsons MW. Whole-Brain CT Perfusion to Quantify Acute Ischemic Penumbra and Core. Radiology 2016;279:876-87.

40. Parthasarathy R, Kate M, Rempel JL, Liebeskind DS, Jeerakathil T, Butcher KS, et al. Prognostic evaluation based on cortical vein score difference in stroke. Stroke 2013;44:2748-54.

41. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.

42. Weimar C, Konig IR, Kraywinkel K, Ziegler A, Diener HC. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. Stroke 2004 ;35:158-62.

"Figures 1, 2, 3 and 5 are reprinted from the article Multimodal CT techniques for cerebro-vascular and hemodynamic evaluation of ischemic stroke. Jia et al. Expert Rev Neurother. 2016;16:515-25, with permission from Taylor and Francis, www.tandfonline.com."