# CT PERFUSION ASSESSMENT OF TREATMENT RESPONSE AND COMPLICATIONS IN ACUTE ISCHEMIC STROKE

ALEXANDER D. HORSCH

**CT PERFUSION ASSESSMENT OF TREATMENT RESPONSE AND COMPLICATIONS IN ACUTE ISCHEMIC STROKE**

PhD thesis, Utrecht University, The Netherlands
ISBN: 978-94-6299-425-6


| | |
|---|---|
| Author: | Alexander Horsch |
| Layout and cover design: | Alexander Horsch (cover image adapted from photo by Christopher Cotrell taken in Alvord Desert, Harney County, Oregon) |
| Print: | Ridderprint BV |

# CT PERFUSION ASSESSMENT OF TREATMENT RESPONSE AND COMPLICATIONS IN ACUTE ISCHEMIC STROKE

**CT-perfusie voor evaluatie van behandeling en complicaties bij een acuut herseninfarct**
(met een samenvatting in het Nederlands)

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 25 oktober 2016
des middags te 12.45 uur

door

**Alexander Darius Horsch**

geboren op
21 juni 1971 te Voorburg

**Promotoren:**

Prof. dr. W.P.Th.M. Mali
Prof. dr. Y. van der Graaf

**Copromotoren:**

Dr. B.K. Velthuis
Dr. J.W. Dankbaar

The research described in this thesis was supported by grants of the Dutch Heart Foundation (2008T034 and 2012T061). Additional funding was provided by a grant of the NutsOhra Foundation (0903-012).

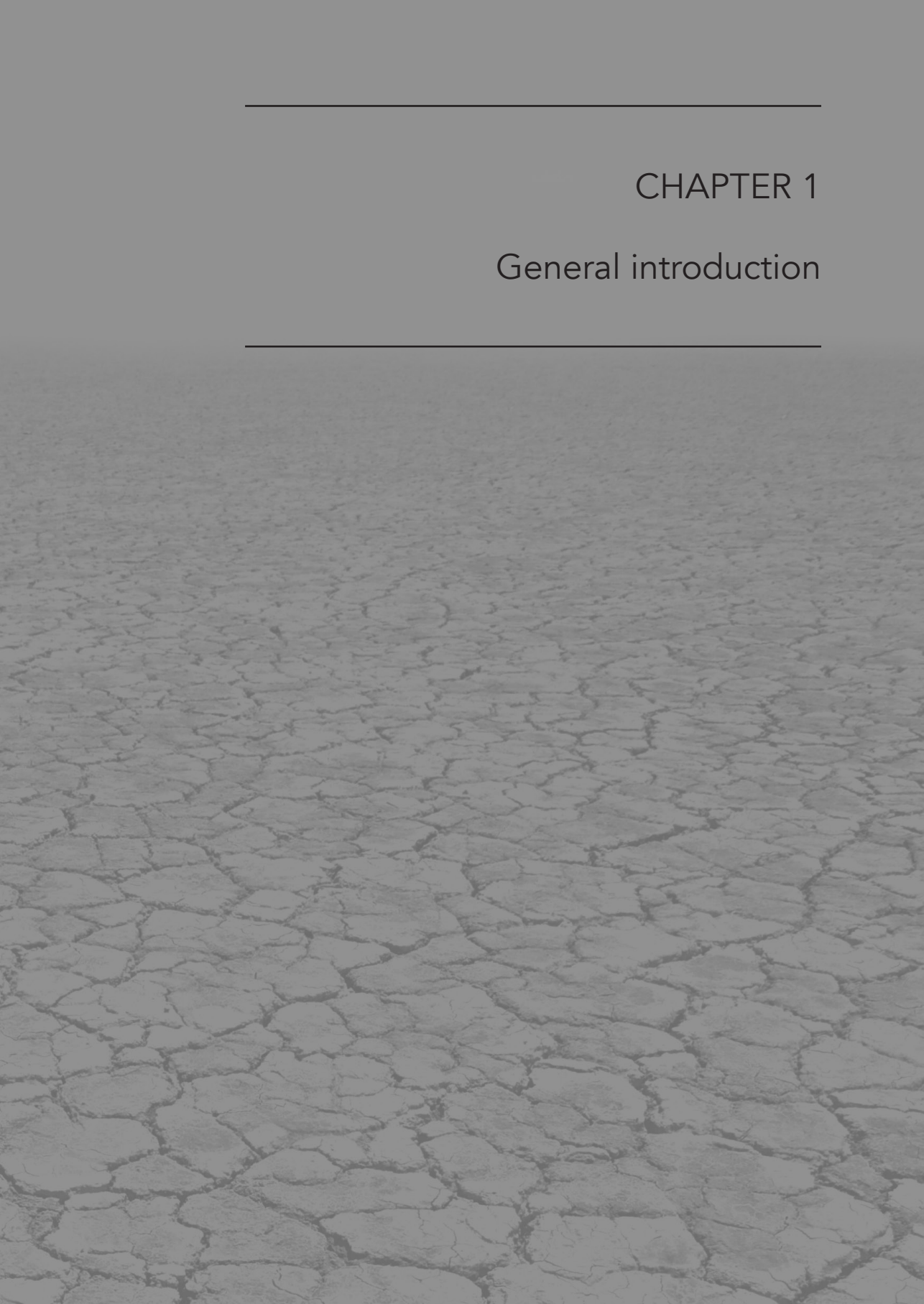
Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged. Additional financial support for the publication of this thesis was generously provided by Philips Healthcare.

# CONTENTS


| | | |
|---|---|---|
| Chapter 1 | General introduction (including list of abbreviations) | 9 |
| Part 1 | Reperfusion and blood-brain barrier permeability | |
| Chapter 2 | Predictors of reperfusion in patients with acute Ischemic stroke | 29 |
| Chapter 3 | Relation between stroke severity, patient characteristics and CT-perfusion derived blood-brain barrier permeability measurements in acute ischemic stroke | 49 |
| Part 2 | Hemorrhagic transformation | |
| Chapter 4 | Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke | 67 |
| Chapter 5 | CT perfusion analysis by nonlinear regression for predicting hemorrhagic transformation in ischemic stroke | 81 |
| Chapter 6 | Can blood-brain barrier CT perfusion derived permeability measurements predict hemorrhagic transformation in acute ischemic stroke? | 103 |
| Part 3 | Malignant edema | |
| Chapter 7 | Imaging findings associated with space-occupying edema in patients with large middle cerebral artery infarcts | 117 |
| Chapter 8 | Blood-brain barrier permeability measurements with CT perfusion predict prominent edema in acute ischemic stroke | 135 |
| Chapter 9 | Summary and general discussion | 153 |
| | Samenvatting | 169 |
| Chapter 10 | Affiliations | 177 |
| | List of publications | 185 |
| | Dankwoord | 193 |
| | Biography | 199 |

# CHAPTER 1

# General introduction



1

# General introduction

## Ischemic stroke

Acute ischemic stroke is a potentially devastating disease caused by the acute occlusion of one of the cerebral arteries leading to infarction of a part of the brain. It has been described as early as 3000 BC, and the number of publications indexed with 'ischemic stroke' on Pubmed reached 70.000 in June 2016.[1] In The Netherlands in 2012, around 20.000 patients were admitted with an acute ischemic stroke and nearly 6.000 died due to this disease.[2] The incidence of acute ischemic stroke has not changed much in the last 10 years, but the number of ischemic stroke deaths has declined since 2002. As a consequence, more patients survive with long term disability. This means that the costs related to this long term disability will probably rise.[2] In the United States, the total direct medical stroke related costs are expected to triple between 2012 and 2030 to 184 billion US dollars.[3]

The symptoms caused by acute ischemic stroke depend on the location of the occlusion and the available collateral circulation. Symptoms can be completely absent or range from relatively minor and unilateral symptoms, to more severe and bilateral deficits. The main cause of acute ischemic stroke is atherosclerosis. This can cause different types of stroke and can be categorized into embolic (thrombus travels to occlusion site), thrombotic (thrombus forms at occlusion site) and dissection (layers of a proximal vessel split and cause an occlusion), or according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[4, 5] There are many risk factors for atherosclerosis of which hypertension is one of the most important. Other risk factors related to ischemic stroke occurrence are a history of previous stroke or transient ischemic attack, hypertension, diabetes and heart disease (atrial fibrillation, valve disease, myocardial infarction, congestive heart failure). Preventable risk factors are smoking, obesity, high cholesterol, elevated lipids, physical inactivity and alcohol intake. Other, unchangeable, factors related to ischemic stroke are older age and sex.[6] Stroke can have a detrimental effect on the daily lives and wellbeing of patients.[6]

## Imaging

Patients presenting in the emergency department with symptoms of acute ischemic stroke will undergo urgent imaging. This is currently done with CT in 80% of hospitals in Europe.[7] The first aim of acute imaging, with non-contrast CT (NCCT), is to exclude other causes for the symptoms such as a primary intra-cerebral hemorrhage or tumor. This is increasingly supplemented with CT angiography (CTA) and, to a lesser degree, with CT perfusion (CTP). CTA supplies information on the presence and location of a thrombus and the available collateral and anastomotic blood supply, which provides important information for the pre-operative assessment for intra-arterial thrombectomy (IAT).[8-12] CTP can provide information

on tissue damage with maps of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP).[13] A relatively new parameter obtained from CTP is the measurement of blood-brain barrier permeability (BBBP).[14-19] CTA and CTP scans can also be performed after treatment and provide valuable information for treatment evaluation by assessment of recanalization and reperfusion status.

## Blood-brain barrier permeability (BBBP)

The blood-brain barrier (BBB) regulates diffusion between the endovascular space and the central nervous system.[20] This barrier is mainly regulated by the endothelial tight junctions of the endothelial cells of the intra-cerebral capillaries but pericytes, astrocytes, neurons and the extra-cellular matrix also play a role.[20] Damage to the blood-brain barrier has been implicated in the development of hemorrhagic transformation (HT) and space-occupying edema in acute ischemic stroke, with increased blood-brain barrier permeability causing leakage of fluid and macromolecules, and even erythrocytes in the case of hemorrhagic transformation.[20] The thrombolytic drug recombinant tissue Plasminogen Activator (rtPA) has also been associated with increased blood-brain barrier permeability due to its direct toxic effects.[21]

Blood-brain barrier permeability can be estimated with MRI and CT imaging.[22] The contrast leaks through the damaged blood-brain barrier into the extra-vascular space and this can be quantified with CTP. The relationship between patient characteristics, stroke severity and blood-brain barrier permeability values needs to be investigated before blood-brain barrier permeability can be evaluated as a clinical tool for the prediction of hemorrhagic transformation or malignant edema. Additionally, the reproducibility of blood-brain barrier permeability measurements is unclear.

Several CTP studies have revealed a relation between increased blood-brain barrier permeability and the occurrence of hemorrhagic transformation.[14, 23-26] The relation between increased blood-brain barrier permeability measured with CTP and space-occupying edema has been shown in fewer studies.[25, 27] Some issues with these studies are the relatively small populations with few outcomes and the short duration of the CTP acquisitions. The Patlak model uses as a mathematical abstraction of the perfusion process from the CTP data. A longer acquisition (more than 200 seconds) is important because one of the assumptions of the Patlak model is that it must be applied only after the steady-state phase of contrast transfer between the intra-vascular and extra-vascular compartments has been reached.[17] The Patlak model is very sensitive to small fluctuations in the noise or in the signal. Therefore, a new tool has been created in our institution, based on nonlinear regression, and shown to produce more robust and reliable blood-brain barrier permeability estimates compared to the Patlak model.[28]

## Treatment

Intra-venous thrombolysis (IVT) with rtPA is given up to 4.5 hours after onset of the neurological deficits, but should be given as soon as possible to increase the odds of a good outcome.[29-33] However, recanalization with intra-venous thrombolysis is only achieved in 50% of patients.[34] Recently, multiple randomized clinical trials showed that stent retriever intra-arterial thrombectomy within 6 hours improves outcome.[35-39] A major risk of both intra-venous thrombolysis and intra-arterial thrombectomy is the occurrence of hemorrhagic transformation, whereby a hemorrhage develops in the area of the infarct.[29-33, 35-39]

## Reperfusion and recanalization

The main aim of the intra-venous thrombolysis and intra-arterial thrombectomy is resolution of the thrombus in the occluded artery territory, which is called revascularization. Revascularization of the vasculature can be divided into 3 components: (1) recanalization of the proximal thrombus; (2) recruitment of the leptomeningeal and circle of Willis collaterals; and (3) reperfusion, the revascularization of the brain capillaries.[40]

The terms reperfusion and recanalization have often been used as synonyms, especially in studies investigating intra-arterial thrombectomy.[41-44] In most randomized clinical trials of intra-arterial thrombectomy, the direct result of the treatment is assessed by the Thrombolysis in Cerebral Infarction (TICI) score, a combined recanalization and reperfusion score, which is obtained by digital subtraction angiography.[35-39, 45] This can lead to confusion, because recanalization does not necessarily lead to reperfusion and improved clinical outcome.[32, 46-49] Additionally, the Thrombolysis in Cerebral Infarction score has not been used consistently in literature.[50] The relation between recanalization and reperfusion, as can be determined with CTA and CTP, deserves further investigation.

## Hemorrhagic transformation (HT)

One of the most devastating complications in acute ischemic stroke, occurring with or without treatment, is the development of hemorrhagic transformation of the infarcted area. Hemorrhagic transformation can be diagnosed with CT or MRI. CT is most commonly used but MRI is more sensitive to detect smaller hemorrhages.[51] Hemorrhagic transformation is classified according to the classification used in European Cooperative Acute Stroke Study (ECASS), with hemorrhagic infarction (HI) type-1 (small petechiae without mass effect) and type-2 (more confluent hyperdensity without mass effect), and parenchymal hemorrhages (PH) type-1 (homogenous hyperdensity with some mass effect, <30% of infarct area) and type-2 (homogenous hyperdensity with significant mass effect, >30% of infarct area).[31, 52] Especially the larger parenchymal hemorrhages type-2 are a major cause of increased morbidity in 50%

of cases, and an increase in mortality up to 9%. In contrast, smaller hemorrhagic infarction types of hemorrhages have also been related to worse long term outcome.[53-55] The percentage of all types of hemorrhagic transformation in patients without any thrombolytic treatment is around 12%, and in clinical practice when intra-venous thrombolysis is given within 3 hours this percentage is also around 12%, but higher numbers up to 40% have been reported.[29, 33, 56-58]

Predictors of hemorrhagic transformation, and parenchymal hemorrhage type-2 in particular, include higher age, higher stroke severity, higher glucose, atrial fibrillation, congestive heart failure, renal impairment, previous antiplatelet agents, leukoaroaiosis and acute ischemic lesion on pre-treatment non-contrast imaging.[59] CT imaging parameters have also been associated with hemorrhagic transformation such as Alberta Stroke Program Early CT Score (ASPECTS) and hyperdense middle cerebral artery (MCA) sign on NCCT, large vessel occlusion and poor collateral score on CTA, and larger infarct volume and total ischemic volume on CTP.[14, 60-63] Thrombolytic agents like rtPA increase the risk of hemorrhagic transformation by their impact on the clotting system.[64] The blood-brain barrier also plays an important role in the development of hemorrhagic transformation.[21] Both the ischemic damage to the brain arteries and possible neurotoxicity of rtPA can cause blood-brain barrier disruption.[21] Early identification of patients who are likely to develop hemorrhagic transformation is one of the major aims of this thesis. If the risk of hemorrhagic transformation could be determined for each individual patient, before intra-venous or intra-arterial treatment is given, a decision could be made to withhold treatment if the risk is deemed to outweigh the benefits.

## Malignant edema (ME)

Another serious complication of acute ischemic stroke is the occurrence of space-occupying edema, also known as malignant edema (ME), with increase in intra-cerebral pressure and midline shift.[65] Although a certain degree of cerebral edema occurs in any acute ischemic stroke, malignant edema usually occurs in large middle cerebral artery infarcts. Large middle cerebral artery strokes occur in around 10% of supratentorial strokes and around 5-10% of these develop malignant edema.[65] This edema can cause further compression of adjacent non-ischemic areas and increased neurological deterioration. Both cytotoxic and vasogenic components have been implicated in the formation of malignant edema. In the ischemic area the cells attempt to maintain homeostasis and accumulate intra-cellular fluid (cytotoxic edema). This eventually leads to the disruption of the blood-brain barrier and the vasogenic component becomes more important. In reality, this process is much more complex and does not perfectly follow this crude division. The mortality of malignant edema reaches 80%, despite optimal medical management.[66]

Main factors related to malignant edema are higher National Institutes of Health Stroke Scale (NIHSS) on admission, younger age, more proximal and extensive occlusion (middle cerebral artery occlusion with an additional territory occlusion), poor collateral supply, larger infarct volume size, reduced intra-cranial volume reserve.[67-70]

The only treatment for malignant edema is decompressive craniectomy which reduces the rate of mortality, although a high percentage of surviving patients suffer severe disability.[71-73] Not all large hemispheric strokes develop malignant edema and risk stratification is important because the outcome of decompressive craniectomy is better if implemented early, before irreversible swelling occurs. Early identification of individual patients who are likely to develop malignant edema is a second important aim of this thesis.

1

# Summary of variables related to ischemic stroke and complications.

The interaction of the different variables involved in the occurrence hemorrhagic transformation and malignant edema is complex and the causes are multifactorial. Patient and stroke related factors, including imaging parameters, and type and timing of treatment all play a role in the development of these severe complications (see Figure 1).

Further knowledge of the relation between these variables and the occurrence of complications in acute ischemic stroke, and their ability to predict these complications could improve stroke outcomes.

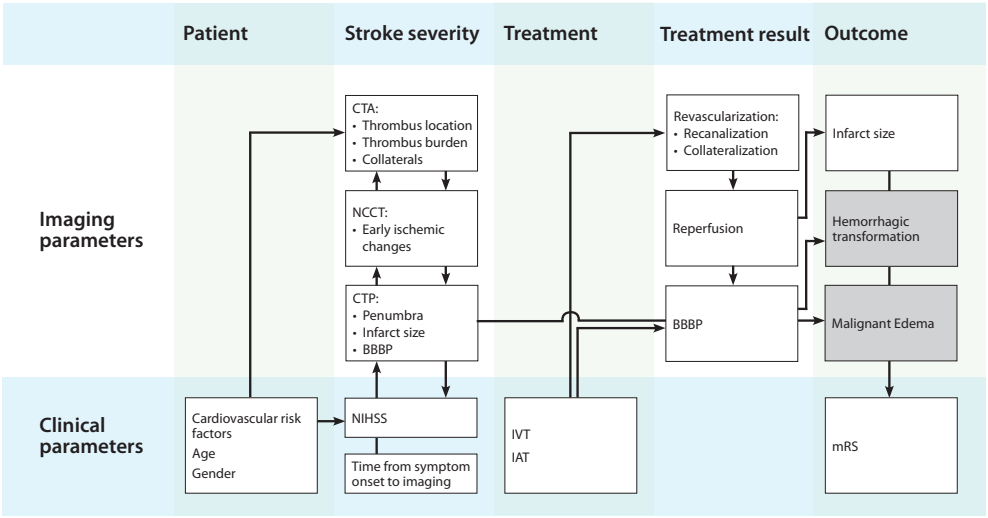



Figure 1.

BBBP, blood-brain barrier; CTA, CT angiography; CTP, CT perfusion; IAT, intra-arterial thrombectomy; IVT, intra-venous thrombolysis; mRS, modified Rankin Score; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale.

# Aims and outlines of this thesis

The general aim of this thesis is to improve the prediction of two severe complications in acute ischemic stroke (hemorrhagic transformation and malignant edema) with advanced CT imaging, and with CTP and blood-brain barrier permeability measurements in particular.

In **chapter 2** we investigate the relationship between recanalization and reperfusion and identify predictors of reperfusion. In **chapter 3** we focused on the influence of imaging and patient characteristics on admission blood-brain barrier permeability values calculated with the Patlak model. In **chapter 4** the relationship between reperfusion and the occurrence of hemorrhagic transformation was investigated. A new method of predicting hemorrhagic transformation with blood-brain barrier permeability values obtained from a nonlinear regression model was first tested in a small group of patients in **chapter 5**, and in **chapter 6** the additional value of this method was assessed in the Dutch acute stroke study (DUST) population. In **chapter 7** we investigated patients with large infarcts on follow-up and tried to clarify why some patients developed space-occupying edema while others do not, and in **chapter 8** the additional value of the new model in predicting this space-occupying edema was investigated. **Chapter 9** provides a summary and general discussion.

# List of abbreviations

| | |
|---|---|
| a | Adjusted |
| ACA | Anterior cerebral artery |
| AIF | Arterial input function |
| ASPECTS | Alberta Stroke Program Early CT Score |
| AUC | Area under the curve |
| BAT | Bolus arrival time |
| BBB | Blood-brain barrier |
| BBBP | Blood-brain barrier permeability |
| CBF | Cerebral blood flow |
| CBS | Clot burden score |
| CBV | Cerebral blood volume |
| CI | Confidence interval |
| CT | Computed tomography |
| CTA | CT angiography |
| CTP | CT perfusion |
| DCE | Dynamic contrast enhancement |
| DUST | Dutch acute stroke study |
| DVS | Dense vessel sign |
| DWI | Diffusion weighted imaging |
| ECASS | European Cooperative Acute Stroke Study |
| ECTS | Early CT signs |
| FWHM | Full width at half maximum |
| HI | Hemorrhagic infarction |
| HT | Hemorrhagic transformation |
| HU | Hounsfield units |
| IAT | Intra-arterial treatment |
| ICA | Internal carotid artery |
| IQ | Interquartile range |

| | |
|---|---|
| IRF | Impulse response function |
| IVT | Intra-venous thrombolysis |
| $K^{trans}$ | Permeability transfer constant |
| MCA | Middle cerebral artery |
| ME | Malignant edema |
| MRI | Magnetic resonance imaging |
| mRS | Modified Rankin Score |
| MT | Mechanical thrombectomy |
| MTT | Mean transit time |
| NCCT | Non-contrast CT |
| NIHSS | National Institutes of Health Stroke Scale |
| NLR | Nonlinear regression |
| NPV | Negative predictive value |
| OR | Odds ratio |
| PH | Parenchymal hemorrhage |
| PPV | Positive predictive value |
| PS | Permeability-surface area product |
| r | Relative |
| ROC | Receiver operating characteristics curve |
| ROI | Region of interest |
| RR | Relative risk |
| rtPA | Recombinant tissue Plasminogen Activator |
| SD | Standard deviation |
| TAC | Time attenuation curve |
| TICI | Thrombolysis in cerebral infarction score |
| TIMI | Thrombolysis in myocardial infarction score |
| TTP | Time to peak |

# References


1. Greer DM. Acute ischemic stroke: an evidence-based approach. Hoboken, New Jersey. John Wiley & Sons, Inc. 2007.

2. Hartstichting. Hart- en vaatziekten in Nederland 2013. Cijfers over leeftstijl, risicofactoren, ziekte en sterfte. 2013

3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation. 2014;129:e28-e292

4. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32:2735-2740

5. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke.1993;24:35-41

6. Victor M, Ropper A. Adams and Victor's, Principles of Neurology 7th Edition. 2001

7. Wintermark M, Luby M, Bornstein NM, Demchuk A, Fiehler J, Kudo K, Lees KR, Liebeskind DS, Michel P, Nogueira RG, Parsons MW, Sasaki M, Wardlaw JM, Wu O, Zhang W, Zhu G, Warach SJ. International survey of acute stroke imaging used to make revascularization treatment decisions. Int J Stroke. 2015;10:759-762

8. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, O'Reilly C, Hudon ME, Hu WY, Coutts SB, Barber PA, Watson T, Roy J, Demchuk AM. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3:230-236

9. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. AJNR Am J Neuroradiol. 2009;30:525-531

10. Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. AJNR Am J Neuroradiol. 2005;26:1789-1797

11. Angermaier A, Langner S, Kirsch M, Kessler C, Hosten N, Khaw AV. CT-angiographic collateralization predicts final infarct volume after intra-arterial thrombolysis for acute anterior circulation ischemic stroke. Cerebrovasc Dis. 2011;31:177-184

12. Lima FO, Furie KL, Silva GS, Lev MH, Camargo EC, Singhal AB, Harris GJ, Halpern EF, Koroshetz WJ, Smith WS, Yoo AJ, Nogueira RG. The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. Stroke. 2010;41:2316-2322

13. Biesbroek JM, Niesten JM, Dankbaar JW, Biessels GJ, Velthuis BK, Reitsma JB, van der Schaaf IC. Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2013;35:493-501

14. Aviv RI, d'Esterre CD, Murphy BD, Hopyan JJ, Buck B, Mallia G, Li V, Zhang L, Symons SP, Lee TY. Hemorrhagic transformation of ischemic stroke: prediction with CT perfusion. Radiology. 2009;250:867-877

15. Bisdas S, Hartel M, Cheong LH, Koh TS. Detection of Early Vessel Leakiness in Acute Ischemic Stroke Using Computed Tomography Perfusion May Indicate Hemorrhagic Transformation. Acta Radiologica. 2007;48:341-344

16. Dankbaar JW, Hom J, Schneider T, Cheng SC, Bredno J, Lau BC, van der Schaaf IC, Wintermark M. Dynamic perfusion-CT assessment of early changes in blood brain barrier permeability of acute ischaemic stroke patients. J Neuroradiol. 2011;38:161-166

17. Dankbaar JW, Hom J, Schneider T, Cheng SC, Lau BC, van der Schaaf I, Virmani S, Pohlman S, Dillon WP, Wintermark M. Dynamic Perfusion CT Assessment of the Blood-Brain Barrier Permeability: First Pass versus Delayed Acquisition. AJNR Am J Neuroradiol. 2008;29:1671-1676

18. Dankbaar JW, Hom J, Schneider T, Cheng SC, Lau BC, van der Schaaf I, Virmani S, Pohlman S, Wintermark M. Age- and anatomy-related values of blood-brain barrier permeability measured by perfusion-CT in non-stroke patients. J Neuroradiol. 2009;36:219-227

19. Dankbaar JW, Hom J, Schneider T, Cheng S-C, Lau BC, van der Schaaf I, Virmani S, Pohlman S, Dillon WP, Wintermark M. Accuracy and Anatomical Coverage of Perfusion CT Assessment of the Blood-Brain Barrier Permeability: One Bolus versus Two Boluses. Cerebrovasc Dis. 2008;26:600-605

20. Sandoval KE, Witt KA. Blood-brain barrier tight junction permeability and ischemic stroke. Neurobiol Dis. 2008;32:200-219

21. Abu Fanne R, Nassar T, Yarovoi S, Rayan A, Lamensdorf I, Karakoveski M, Vadim P, Jammal M, Cines DB, Higazi AA. Blood-brain barrier permeability and tPA-mediated neurotoxicity. Neuropharmacology. 2010;58:972-980

22. Kassner A, Mandell DM, Mikulis DJ. Measuring permeability in acute ischemic stroke. Neuroimaging Clin N Am. 2011;21:315-325, x-xi

23. Bisdas S, Hartel M, Cheong LH, Koh TS, Vogl TJ. Prediction of subsequent hemorrhage in acute ischemic stroke using permeability CT imaging and a distributed parameter tracer kinetic model. J Neuroradiol. 2007;34:101-108

24. Ozkul-Wermester O, Guegan-Massardier E, Triquenot A, Borden A, Perot G, Gerardin E.

Increased blood-brain barrier permeability on perfusion computed tomography predicts hemorrhagic transformation in acute ischemic stroke. Eur Neurol. 2014;72:45-53

25. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, Lau BC, Smith W, Dillon WP, Wintermark M. Blood-Brain Barrier Permeability Assessed by Perfusion CT Predicts Symptomatic Hemorrhagic Transformation and Malignant Edema in Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2011;32:41-48

26. Lin K, Kazmi KS, Law M, Babb J, Peccerelli N, Pramanik BK. Measuring Elevated Microvascular Permeability and Predicting Hemorrhagic Transformation in Acute Ischemic Stroke Using First-Pass Dynamic Perfusion CT Imaging. AJNR Am J Neuroradiol. 2007;28:1292-1298

27. Bektas H, Wu TC, Kasam M, Harun N, Sitton CW, Grotta JC, Savitz SI. Increased blood-brain barrier permeability on perfusion CT might predict malignant middle cerebral artery infarction. Stroke. 2010;41:2539-2544

28. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751

29. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375:1695-1703

30. NINDS rssg. 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;333:1581-1587

31. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025

32. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7:299-309

33. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275-282

34. Mazighi M, Serfaty JM, Labreuche J, Laissy JP, Meseguer E, Lavallee PC, Cabrejo L, Slaoui T, Guidoux C, Lapergue B, Klein IF, Olivot JM, Abboud H, Simon O, Niclot P, Nifle C, Touboul PJ, Raphaeli G, Gohin C, Claeys ES, Amarenco P. Comparison of intravenous alteplase with

a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. The Lancet. Neurology. 2009;8:802-809

35. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, Clark W, Budzik R, Zaidat OO. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet. 2012;380:1241-1249

36. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11-20

37. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009-1018

38. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallofre M, Davalos A. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296-2306

39. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019-1030

40. Wintermark M, Warach SJ. Acute Stroke Imaging Research Roadmap II and International Survey of Acute Stroke Imaging Capabilities: We Need Your Help! AJNR Am J Neuroradiol. 2013;34:1671

41. Murphy A, Symons SP, Hopyan J, Aviv RI. Factors influencing clinically meaningful recanalization after IV-rtPA in acute ischemic stroke. AJNR Am J Neuroradiol. 2013;34:146-152

42. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. Stroke. 2006;37:1227-1231

43. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke. 2005;36:66-73

44. Fiehler J, Remmele C, Kucinski T, Rosenkranz M, Thomalla G, Weiller C, Zeumer H, Rother J. Reperfusion after severe local perfusion deficit precedes hemorrhagic transformation: an MRI study in acute stroke patients. Cerebrovasc Dis. 2005;19:117-124

45. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003;34:e109-137

46. Eilaghi A, Brooks J, d'Esterre C, Zhang L, Swartz RH, Lee TY, Aviv RI. Reperfusion Is a Stronger Predictor of Good Clinical Outcome than Recanalization in Ischemic Stroke. Radiology. 2013; Oct;269(1):240-8

47. De Silva DA, Fink JN, Christensen S, Ebinger M, Bladin C, Levi CR, Parsons M, Butcher K, Barber PA, Donnan GA, Davis SM. Assessing reperfusion and recanalization as markers of clinical outcomes after intravenous thrombolysis in the echoplanar imaging thrombolytic evaluation trial (EPITHET). Stroke. 2009;40:2872-2874

48. Yoo AJ. Revascularization Grading: The Devil Is in the Details. Radiology. 2013;269:6-7

49. Soares BP, Tong E, Hom J, Cheng SC, Bredno J, Boussel L, Smith WS, Wintermark M. Reperfusion is a more accurate predictor of follow-up infarct volume than recanalization: a proof of concept using CT in acute ischemic stroke patients. Stroke. 2010;41:e34-40

50. Fugate JE, Klunder AM, Kallmes DF. What is meant by "TICI"? AJNR Am J Neuroradiol. 2013;34:1792-1797

51. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, Butman JA, Patronas N, Alger JR, Latour LL, Luby ML, Baird AE, Leary MC, Tremwel M, Ovbiagele B, Fredieu A, Suzuki S, Villablanca JP, Davis S, Dunn B, Todd JW, Ezzeddine MA, Haymore J, Lynch JK, Davis L, Warach S. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA. 2004;292:1823-1830

52. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, Ringleb AP, Lorenzano S, Manelfe C, Bozzao L. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke. 1999;30:2280-2284

53. Strbian D, Sairanen T, Meretoja A, Pitkaniemi J, Putaala J, Salonen O, Silvennoinen H, Kaste M, Tatlisumak T. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. Neurology. 2011;77:341-348

54. Kimura K, Iguchi Y, Shibazaki K, Aoki J, Terasawa Y. Hemorrhagic transformation of ischemic brain tissue after t-PA thrombolysis as detected by MRI may be asymptomatic, but impair neurological recovery. J Neurol Sci. 2008;272:136-142

55. Park JH, Ko Y, Kim WJ, Jang MS, Yang MH, Han MK, Oh CW, Park SH, Lee J, Bae HJ, Gorelick PB. Is asymptomatic hemorrhagic transformation really innocuous? Neurology. 2012;78:421-426

56. Terruso V, D'Amelio M, Di Benedetto N, Lupo I, Saia V, Famoso G, Mazzola MA, Aridon P, Sarno C, Ragonese P, Savettieri G. Frequency and determinants for hemorrhagic transformation of cerebral infarction. Neuroepidemiology. 2009;33:261-265

57. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke. 2003;34:2847-2850

58. Sussman ES, Connolly ES, Jr. Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol. 2013;4:69

59. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke. 2012;43:2904-2909

60. Lin K, Zink WE, Tsiouris AJ, John M, Tekchandani L, Sanelli PC. Risk Assessment of Hemorrhagic Transformation of Acute Middle Cerebral Artery Stroke Using Multimodal CT. J Neuroimaging. 2012;22:160-166

61. Jain AR, Jain M, Kanthala AR, Damania D, Stead LG, Wang HZ, Jahromi BS. Association of CT perfusion parameters with hemorrhagic transformation in acute ischemic stroke. AJNR Am J Neuroradiol. 2013;34:1895-1900

62. Souza LC, Payabvash S, Wang Y, Kamalian S, Schaefer P, Gonzalez RG, Furie KL, Lev MH. Admission CT Perfusion Is an Independent Predictor of Hemorrhagic Transformation in Acute Stroke with Similar Accuracy to DWI. Cerebrovasc Dis. 2012;33:8-15

63. Yassi N, Parsons MW, Christensen S, Sharma G, Bivard A, Donnan GA, Levi CR, Desmond PM, Davis SM, Campbell BC. Prediction of Poststroke Hemorrhagic Transformation Using Computed Tomography Perfusion. Stroke. 2013 Nov;44(11):3039-43

64. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, Cohen G. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012;379:2364-2372

65. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53:309-315

66. Flint AC, Faigeles BS, Cullen SP, Kamel H, Rao VA, Gupta R, Smith WS, Bath PM, Donnan GA. THRIVE Score Predicts Ischemic Stroke Outcomes and Thrombolytic Hemorrhage Risk in VISTA. Stroke. 2013;44:3365-3369

67. Sykora M, Steiner T, Rocco A, Turcani P, Hacke W, Diedler J. Baroreflex sensitivity to predict

malignant middle cerebral artery infarction. Stroke. 2012;43:714-719

68. Walcott BP, Miller JC, Kwon CS, Sheth SA, Hiller M, Cronin CA, Schwamm LH, Simard JM, Kahle KT, Kimberly WT, Sheth KN. Outcomes in Severe Middle Cerebral Artery Ischemic Stroke. Neurocrit Care. 2014;21:20-26

69. Thornhill RE, Chen S, Rammo W, Mikulis DJ, Kassner A. Contrast-Enhanced MR Imaging in Acute Ischemic Stroke: T2* Measures of Blood-Brain Barrier Permeability and Their Relationship to T1 Estimates and Hemorrhagic Transformation. AJNR Am J Neuroradiol. 2010;31:1015-1022

70. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. Cerebrovasc Dis. 2008;25:176-184

71. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurology. 2007;6:215-222

72. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurology. 2009;8:326-333

73. Geurts M, van der Worp HB, Kappelle LJ, Amelink GJ, Algra A, Hofmeijer J. Surgical decompression for space-occupying cerebral infarction: outcomes at 3 years in the randomized HAMLET trial. Stroke. 2013;44:2506-2508

# CHAPTER 2

# Predictors of reperfusion in patients with acute ischemic stroke

Alexander D. Horsch, Jan Willem Dankbaar, Joris M. Niesten, Tom van Seeters, Irene C. van der Schaaf, Y. van der Graaf, Willem P.Th.M. Mali, Birgitta K. Velthuis, on behalf of the Dutch acute stroke study (DUST) Investigators

Adapted from:
**AJNR Am J Neuroradiol 2015;36:1056-1062**

# Abstract

## Background and purpose

Ischemic stroke studies emphasize a difference between reperfusion and recanalization, but predictors of reperfusion have not been elucidated. The aim of this study was to evaluate the relationship between reperfusion and recanalization, and identify predictors of reperfusion.

## Materials and Methods

From the Dutch Acute Stroke Study 178 patients were selected with a middle cerebral artery (MCA) territory deficit on admission CT perfusion (CTP) and day 3 follow-up CTP and CT angiography (CTA). Reperfusion was evaluated on CTP and recanalization on CTA follow-up imaging. Reperfusion percentages were calculated in patients with and without recanalization. Patient admission and treatment characteristics, and admission CT imaging parameters were collected. Their association with complete reperfusion was analyzed using univariate and multivariate logistic regression.

## Results

Sixty percent of patients with complete recanalization showed complete reperfusion (relative risk (RR) 2.60, 95% CI 1.63-4.13). Approximately one third of patients showed some discrepancy between recanalization and reperfusion status. Lower National Institutes of Health Stroke Scale (NIHSS) (odds ratio (OR) 1.06 95% CI 1.01-1.11), smaller infarct core size (OR 3.11 95% CI 1.46-6.66 and 2.40 95% CI 1.14-5.02), smaller total ischemic area (OR 4.20 95% CI 1.91-9.22 and 2.35 95% CI 1.12-4.91), lower clot burden (OR 1.35 95% CI 1.14-1.58), distal thrombus location (OR 3.02 95% CI 1.76-5.20) and good collateral score (OR 2.84 95% CI 1.34-6.02) significantly increased the odds of complete reperfusion. In multivariate analysis, only total ischemic area (OR 6.12 95% CI 2.69-13.93 and 1.91 95% CI 0.91-4.02) was an independent predictor of complete reperfusion.

## Conclusion

Recanalization and reperfusion are strongly associated but not always equivalent in ischemic stroke. A smaller total ischemic area is the only independent predictor of complete reperfusion.

# Introduction

Patients with acute ischemic stroke presenting within 4.5 hours are treated with intravenous recombinant tissue Plasminogen Activator (IV-rtPA) to dissolve the thrombus and achieve revascularization.[1] A recent consensus meeting on stroke imaging research (Acute Stroke Imaging Research Roadmap II) suggests that revascularization is a combination of three different mechanisms; (1) recanalization, referring to arterial patency; (2) reperfusion, which refers to antegrade microvascular perfusion; and (3) collateralization, which refers to microvascular perfusion via pial arteries or other anastomotic arterial channels that bypass the primary site of vessel occlusion.[2] Recanalization, reperfusion and collateralization can be evaluated by CT angiography (CTA) and CT perfusion (CTP), which are frequently used in dedicated stroke imaging protocols. An important reason to look at the revascularization mechanisms separately is the concept that recanalization of an arterial occlusion as visualized on CTA does not necessarily lead to complete reperfusion and improved clinical outcome.[3, 4] Furthermore, reperfusion can also occur without afferent vessel recanalization through collateralization of the ischemic area by collateral flow.[5, 6]

Many previous studies, including those investigating intra-arterial therapy, consider recanalization to be synonymous to reperfusion.[7-10] Other papers suggest this assumption is not justified and found reperfusion to be a better predictor of follow-up infarct volume and clinical outcome than recanalization.[5, 8, 9, 11-15]

Although recanalization correlates well with improved reperfusion rates, it is unclear which other clinical and imaging factors influence reperfusion.[5, 6, 11, 12, 16] Knowing which factors, available prior to treatment decisions, predict complete reperfusion could aid decision making. Treatment with IV-rtPA, good collateral scores as well as lesion geography (location of the infarct relative to penumbra) and structure (solitary or multiple infarct areas) have been related to reperfusion status assessed with CT or MR imaging.[5, 15, 17-19]

The aim of this study was to evaluate the relationship between reperfusion and recanalization and to investigate which clinical and CT imaging parameters, available on admission, can help predict complete reperfusion in acute ischemic stroke patients.

# Materials and methods

## Study design

The Dutch acute stroke study (DUST) is a large prospective multicenter cohort study, which aims to assess the additional value of CTP and CTA in predicting outcome of patients with acute ischemic stroke. The study protocol has been published previously.[20] In brief, inclusion criteria for this study were: age ≥18 years, suspected acute ischemic stroke of < 9 hours'

duration, and a National Institutes of Health Stroke Scale (NIHSS) ≥2 (or 1 if an indication for IV-rtPA was present). Exclusion criteria were known renal failure, contraindications to iodinated contrast material, and the presence of another diagnosis on admission non -contrast CT (NCCT) that explained the symptoms. This study was approved by the local institutional ethical review boards of the participating centers. All patients or family gave signed informed consent, unless a patient died before consent could be obtained. In that case, the need for consent was waived by the medical ethics committee.[20]

## Patient selection

From the DUST database, a consecutive series of patients included between May 2009 and August 2012 was selected from 9 centers. Additional inclusion criteria for this study were the following: 1) perfusion deficit in the middle cerebral artery (MCA) territory on admission CTP, and 2) available admission and follow-up CTP and CTA. Exclusion criteria were: 1) poor quality CTP or CTA, 2) absence of 1 of the 2 Alberta Stroke Program Early CT Score (ASPECTS) levels on admission CTP or 3) use of intra-arterial treatment. The inclusion process is clarified in the flow chart (Figure 1).

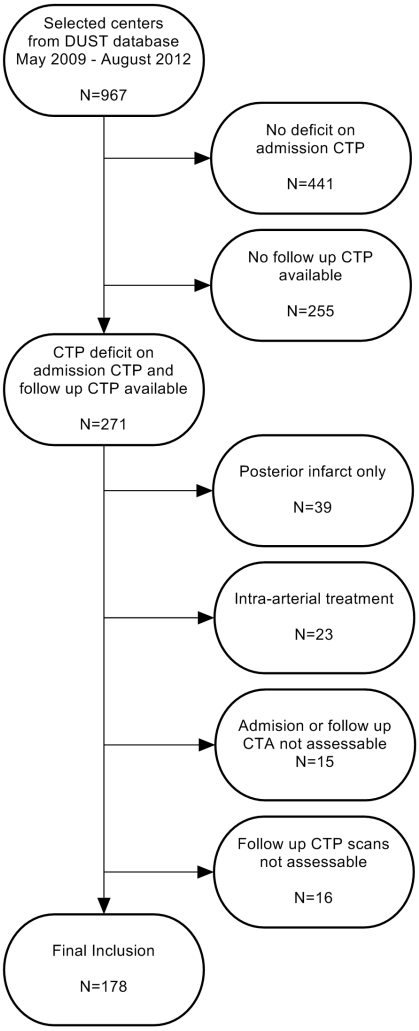



Figure 1. Inclusion flow chart

## Predictor selection

Clinical variables that were collected included: age, sex, history of stroke, admission NIHSS score, IV-rtPA treatment and time from symptom onset to treatment. Admission imaging variables included the following: infarct core size and total ischemic area from CTP ASPECTS levels, and clot burden (clot burden score), thrombus location (internal carotid artery (ICA), MCA-M1 segment, MCA-M2 segment and >M2) and collateral score from CTA.

## Imaging protocol

NCCT, CTP, and CTA of the cervical and cerebral vessel were performed on admission.

Multi-detector CT scanners were used with number of detectors ranging from 40 to 320 (Brilliance 40, Brilliance 64, Brilliance iCT 256; Philips Healthcare, Best, The Netherlands, Sensation 64, Siemens, Erlangen, Germany; Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan). NCCT was performed with 120 kV, 300-375 mAs, and slice thickness of 5 mm.[20]

The CTP, performed with 80 kV and 150 mAs, involved successive gantry rotations in cine mode during intra-venous administration of 40 ml non-ionic contrast material followed by 40ml of saline with a flow of 6ml/sec.[20] CTP coverage included at least the level of the basal ganglia to the lateral ventricles to be able to assess both ASPECTS levels.[21]

The CTA was acquired from aortic arch to the vertex with 50-70 ml contrast followed by 40 ml of saline, both with a flow of 6 ml/s. The individual CTA scan delay after intra-venous injection was calculated from time to peak arterial enhancement on CTP, or by trigger-based Hounsfield threshold measurement of contrast enhancement in the aortic arch.[20]

## Imaging analysis

CTP: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) were automatically calculated from CTP data using commercially available CTP software (Extended Brilliance Workstation 4.5; Philips Healthcare). The non-occluded ICA or anterior cerebral artery was chosen as arterial input function.[22] The superior sagittal sinus was used as venous output function. The presence of a perfusion deficit on admission was defined as a focal asymmetry on the CBF, CBV, MTT or TTP map, matching a part or the whole of the MCA flow territory. The total ischemic area was defined with a MTT threshold of 145% compared to the non-affected side. Within this area a CBV value of less than 2.0 ml/100g was used to define the infarct core.[23] Infarct core size and total size of the ischemic area were calculated at ASPECTS level 1 and 2 on admission CTP. The degree of axial CTP coverage was different between scanners as CTP was performed with CT scanners ranging from 40-detector to 320-detector. This range could potentially underestimate the initial ischemic area or the degree of reperfusion. For this reason, we only used the ASPECTS levels to compare between patients, to exclude major bias from the difference in number of detectors.

The presence of reperfusion was analyzed by visual comparison of the admission CTP parameter maps (CBF, CBV, MTT and TTP) with the follow-up parameter maps. Reperfusion outcome was classified into 2 categories (complete and incomplete reperfusion). Complete reperfusion was defined as the absence of a perfusion deficit on follow-up CTP in the presence of a deficit on admission. All remaining deficits on follow-up CTP, which were not considered to be caused by artifacts, ipsilateral carotid stenosis, or focal hemorrhage, were categorized as incomplete reperfusion. Hyperperfusion was included in the complete reperfusion group and an enlarged or new perfusion deficit in the incomplete reperfusion

group.

Differences in blood pressure between admission and follow-up CTP have not been taken into account in the assessment of reperfusion status because this assessment was done in a qualitative fashion by visual comparison of the 4 CTP maps and not on image based quantitative thresholds. It was not expected that potential small differences in the size of the CTP deficit would have changed the category of reperfusion status.



CTA: Admission CTA provided data on clot burden score, collateral score and intra-cranial thrombus location. Intra-cranial thrombus location was divided into 3 groups (intra-cranial ICA, MCA-M1 segment, and MCA-M2 or more distal occlusion).[24-26] Thrombus location was classified to the most proximal site of occlusion unless there was a combined extra-cranial ICA occlusion and a more distal MCA occlusion with an open ICA top (tandem lesion), which was classified at the level of the MCA occlusion.[27] Recanalization status was defined qualitatively on follow-up CTA scans as complete or incomplete recanalization. All imaging data were evaluated by one of three observers (I.C.v.d.S, B.K.V. and J.W.D), all with at least 5 years of experience in stroke imaging. Only the side of symptoms was provided for the evaluation.

### Statistical analysis

For all analyses, the complete reperfusion group was compared with the incomplete reperfusion group. Similarly, the complete recanalization group was compared with the incomplete recanalization group. To analyze the relation between complete recanalization and complete reperfusion, absolute and relative risks (RRs) were calculated. Potential determinants of complete reperfusion were tested with univariate and multivariate binary logistic regression analysis, and 95% confidence intervals (CI) were calculated. To reduce the potential influence of non-normal distributions, the following variables were recoded into categories on the basis of tertiles: time to treatment (<60 minutes, 60-120 minutes and ≥120 minutes), infarct core size (<300 $mm^2$, 300-1400 $mm^2$ and ≥1400 $mm^2$), and total ischemic area (<2000 $mm^2$, 2000-5000 $mm^2$ and ≥5000 $mm^2$).

For analysis, patients without visible occlusion on CTA were included in the MCA-M2 or more distal occlusion group. All significant predictors in univariate analysis ($p<0.05$) were used in stepwise backward-elimination multivariate regression analysis. Statistical computations were carried out using SPSS 19.0 (IBM, Armonk, NY, USA).

## Results

Inclusion criteria for this study were met in 178 patients (see Figure 1). Not all patients in the DUST received follow-up due to very rapid recovery and discharge before follow-up could

**Table 1. Baseline clinical and imaging characteristics.**

| | All patients N=178 | Incomplete reperfusion N=92 (52%) | Complete reperfusion N=86 (48%) | P-value |
|---|---|---|---|---|
| **Clinical parameters** | | | | |
| Age, mean (SD) | 68 (13) | 68 (14) | 67 (13) | 0.92 |
| Female sex, n (% ) | 69 (39) | 34 (37) | 35 (41) | 0.61 |
| Prior stroke, n (% ) | 35 (20) | 15 (16) | 20 (23) | 0.24 |
| NIHSS, median (IQ) | 9 (5-15) | 12 (5-16) | 8 (4-13) | 0.06 |
| **Treatment** | | | | |
| rtPA, n (%) | 121 (68) | 61 (66) | 60 (70) | 0.62 |
| Time to treatment, minutes, median (IQ) * | 100 (73-130) | 105 (75-127) | 99 (70-151) | 0.89 |
| | | | | |
| **Imaging parameters** | | | | |
| Time to admission scan, minutes, median (IQ) | 105 (66-170) | 105 (71-157) | 105 (61-187) | 0.62 |
| Time to follow-up, days, mean (SD) | 3.2 (1.3) | 3.3 (1.3) | 3.1 (1.2) | 0.19 |
| **CT perfusion** | | | | |
| Size infarct core, $mm^2$, median (IQ) † | 630 (187-1758) | 985 (293-2659) | 479 (115-1332) | 0.002 |
| Size total ischemic area, $mm^2$, median (IQ) † | 3629 (1551-5605) | 4587 (2848-6248) | 2352 (734-4328) | 0.0005 |
| **CT angiography** | | | | |
| Clot burden score, median (IQ) | 8.0 (6.0-9.0) | 8.0 (6.0-9.0) | 9.0 (7.0-9.0) | 0.003 |
| Thrombus location, ICA, n (%) ‡ | 13 (9) | 13 (15) | 0 | 0.01 |
| Thrombus location, M1, n (%) ‡ | 62 (41) | 37 (43) | 25 (38) | 0.01 |
| Thrombus location, M2 or >M2, n (%) ‡ | 77 (51) | 36 (42) | 41 (62) | 0.01 |
| Good collateral score, n (%) § | 137 (77) | 63 (69) | 74 (86) | 0.005 |

* Only 121 IV-rtPA patients.
† Size infarct core and total ischemic area at both ASPECTS levels combined.
‡ Only 152 cases because 26 patients had no visible occlusion on admission CTA.
§ All patients without visible artery occlusion on admission CTA have a good collateral score.

be done, poor condition of the patient, impaired renal function, or absence of permission for follow-up. No significant difference in admission NIHSS was found between patients with or without follow-up CTP and CTA, which suggests that no major pre-selection occurred.

Baseline clinical and imaging characteristics for the 2 reperfusion groups are summarized in Table 1. Mean age was 68 years, 39% was female, median NIHSS was 9, and 68% received IV-rtPA. The infarct core size (479 versus 985 $mm^2$) and total ischemic area size (2352 versus 4587 $mm^2$) were significantly smaller in the complete reperfusion group compared to the incomplete reperfusion group. In addition, the clot burden was significantly lower in the complete reperfusion group (clot burden score, 9 versus 8) and the thrombus was located more distally (M2 or >M2 in 62% versus 42%, respectively). A good collateral score was also significantly more frequent in the complete reperfusion group (86% versus 69%). No ipsilateral ICA-top occlusion was found on admission in the complete reperfusion group versus 15% in the incomplete reperfusion group.

Table 2 shows the relation between reperfusion status and recanalization in 152 patients with a visible occlusion, as well as the reperfusion status in 26 patients without a visible occlusion on admission CTA. Complete reperfusion was found in 60% of patients with complete recanalization and in 23% in the incomplete recanalization group (RR 2.60, 95%CI 1.63-4.13). Approximately one third of patients (32%) showed some discrepancy between recanalization and reperfusion status. Remarkably, complete reperfusion was found with incomplete recanalization (16 patients) and incomplete reperfusion was found despite complete recanalization (33 patients). Two illustrative cases are shown in Figure 2. In the 26 patients without a visible occlusion on admission CTA, most patients (77%) showed complete reperfusion.

The univariate logistic regression analysis is shown in Table 3. Lower NIHSS (OR 1.06 95% CI 1.01-1.11), smaller infarct core size (OR 3.11 95% CI 1.46-6.66 and OR 2.40 95% CI 1.14-5.02), smaller total ischemic area (OR 4.20 95% CI 1.91-9.22 and OR 2.35 95%

**Table 2. Outcome summary: relation between reperfusion and recanalization.**

| **Reperfusion and recanalization (N=152)** | | | |
|---|---|---|---|
| N (% in rows) | **Incomplete reperfusion** | **Complete reperfusion** | Total |
| **Incomplete recanalization** | 53 (77) | 16 (23) | 69 (100) |
| **Complete recanalization** | 33 (40) | 50 (60) | 83 (100) |
| Total | 86 (57) | 66 (43) | 152 (100) |
| **Reperfusion without visible occlusion on admission CT angiography (n=26)** | | | |
| No occlusion on admission | 6 (23) | 20 (77) | 26 (10) |

CI 1.12-4.91), lower clot burden (OR 1.35 95% CI 1.14-1.58), distal thrombus location (OR 3.02 95% CI 1.76-5.20) and good collateral score (OR 2.84 95% CI 1.34-6.02) significantly increased the odds of complete reperfusion. Age, sex or IV-rtPA treatment did

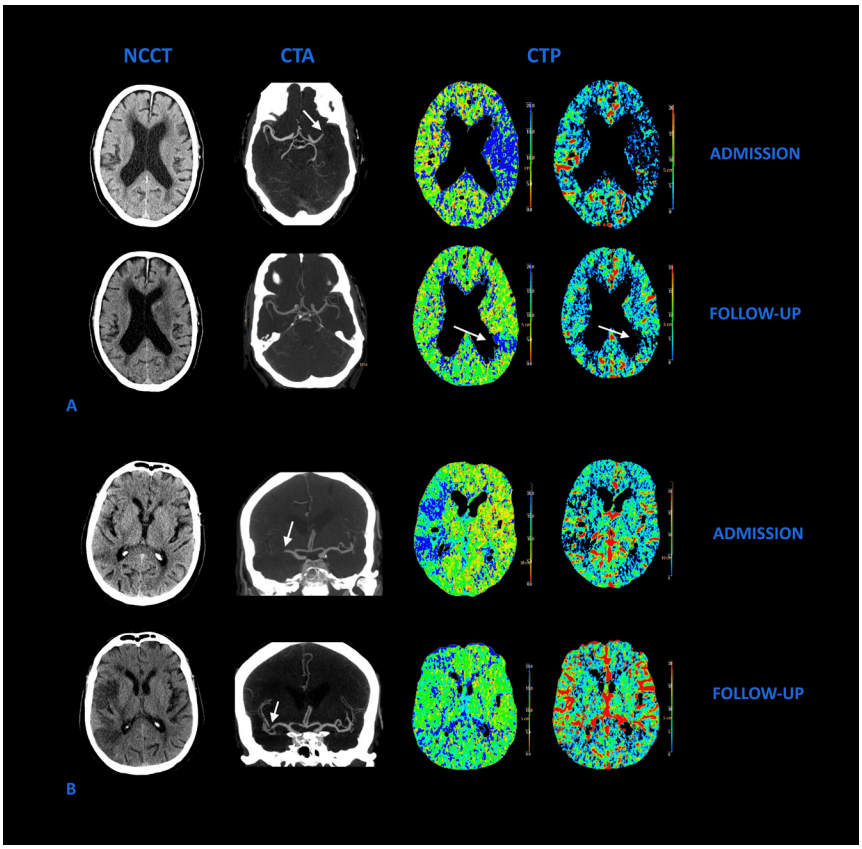



Figure 2: Relation between recanalization and reperfusion.

A. A patient with complete recanalization without complete reperfusion. Admission NCCT shows no early CT signs. Follow-up NCCT shows infarction of the basal ganglia. Admission CTA shows occlusion of the M1 segment (arrow). Follow-up CTA shows complete recanalization; no distal M3 occlusion could be found. Admission CTP shows a large area of decreased MTT and CBV in ASPECTS M5 and M6. Follow-up CTP shows a residual perfusion deficit ASPECTS M6 on the MTT and CBV maps (arrow).

B. A patient with incomplete recanalization but complete reperfusion. Admission NCCT shows some early CT signs in the MCA territory. Follow-up NCCT shows areas of infarction in a large part of the MCA territory. Admission CTA shows an occlusion in the M1 and M2 segments of the MCA. Follow-up CTA shows a short residual occlusion in a M2 segment (arrows). Admission CTP shows a large area of decreased MTT and CBV in ASPECTS M1-M3 which has completely resolved on follow-up.

**Table 3. Predictors of complete reperfusion.**

| N=178 | OR | 95% CI | p-value |
|---|---|---|---|
| **Clinical parameters** | | | |
| Age | 1.00 | 0.98-1.02 | 0.86 |
| Female sex | 1.17 | 0.64-2.14 | 0.61 |
| NIHSS | 1.06 | 1.01-1.11 | 0.03 |
| **Treatment** | | | |
| rtPA | 1.17 | 0.62-2.21 | 0.62 |
| Time to treatment, 60-120 min versus <60 minutes * | 0.54 | 0.17-1.69 | 0.29 |
| Time to treatment, ≥120 minutes versus <60 minutes * | 0.78 | 0.23-2.61 | 0.68 |
| | | | |
| **Imaging parameters** | | | |
| **CT perfusion** | | | |
| Size infarct core, <300 versus ≥1400 $mm^2$ † | 3.11 | 1.46-6.66 | 0.003 |
| Size infarct core, 300-1400 versus ≥1400 $mm^2$ † | 2.40 | 1.14-5.02 | 0.02 |
| Size total ischemic area, <2000 versus ≥5000 $mm^2$ † | 4.20 | 1.91-9.22 | 0.004 |
| Size total ischemic area, 2000-5000 versus ≥5000 $mm^2$ † | 2.35 | 1.12-4.91 | 0.02 |
| **CT angiography** | | | |
| Clot burden score | 1.35 | 1.14-1.58 | 0.001 |
| Thrombus location, ICA, M1 or M2 and >M2 | 3.02 | 1.76-5.20 | 0.006 |
| Good collateral score § | 2.84 | 1.34-6.02 | 0.01 |

Legend: see table 1.

not influence complete reperfusion. In multivariate analysis a smaller total ischemic area (OR 6.12 CI95% 2.69-13.93 and OR 1.91 CI95% 0.91-4.02) was the only independent predictor of complete reperfusion (not shown in Tables).

# Discussion



This study shows that, although reperfusion is strongly related to recanalization in acute ischemic stroke, reperfusion and recanalization do not always occur in unison. An important finding is that none of the patients with an ipsilateral intra-cranial ICA occlusion showed complete reperfusion. Factors that help predict complete reperfusion are lower NIHSS on admission, lower clot burden, more distal thrombus location and a good collateral score (on CTA), and smaller infarct core and smaller total ischemic area (on CTP). In multivariate analysis, only total ischemic area was an independent predictor of complete reperfusion.

## Recanalization versus reperfusion.

The proportion of complete recanalization and complete reperfusion in our study compares to values described in literature, 22-60% for recanalization and 26-79% for reperfusion.[15-18] Our data confirm the suggestion that recanalization and reperfusion are closely related but not interchangeable. The discrepancy of incomplete reperfusion in the presence of complete recanalization can be caused by either the breakup of the primary clot into fragments leading to distal embolization of smaller vasculature not visible on CTA, reversible incomplete microcirculatory reperfusion, or the irreversible no-reflow phenomenon.[3, 28-30] Reperfusion without recanalization of the proximal occlusion is thought to be mediated by collateralization (through pial arteries or other anastomotic channels).[2] Patients without an identifiable occlusion on admission CTA had higher complete reperfusion rates in comparison to patients with a visible occlusion. Undetected micro-thrombi in distal vessels may account for this higher rate because they are more likely to dissolve.

## Predictors of reperfusion

Thrombus location was a predictor of complete reperfusion in our study. Distal MCA occlusions showed better reperfusion rates on follow-up compared with more proximal MCA or ICA top occlusions. A positive relation between distal thrombus location and recanalization has been found in multiple studies.[7, 31-33] In contrast, Lemmens et al. found no relation between distal occlusion and recanalization, though they did find a better clinical response with increased reperfusion.[34] Moreover, none of our patients with an intra-cranial carotid occlusion showed complete reperfusion (despite complete recanalization in 15% and 54% receiving IV-rtPA in this patient group of 13 patients). These findings suggest that those specific patients may need intra-arterial thrombolysis or mechanical thrombectomy. A recent review showed that stenting and mechanical thrombectomy in patients with an intra-

cranial ICA occlusion is associated with higher recanalization rates and better functional outcome.[35]

Few papers describe predictors of brain tissue reperfusion. The most frequently found imaging predictor of reperfusion was recanalization in both CT and MRI studies.[5, 6, 11, 16, 17, 36] However, recanalization is not a variable that can be assessed before treatment. Good collateral scores, treatment with alteplase or tenecteplase, older age, and lesion geography and structure were also associated with better reperfusion.[5, 15, 17-19, 37]

Only total ischemic area was an independent predictor of complete reperfusion in our study. This is not surprising since a smaller size of the total ischemic area is the result of a more distal thrombus location and good collateral status. The effect of these variables is therefore most likely represented by the total ischemic area in our multivariate analysis.

It is unclear why we could not demonstrate a significant relation between IV-rtPA treatment and complete reperfusion. Christoforidis et al. 2005 suggested no benefit from thrombolysis in patients with poor collaterals and more distal occlusion site, but in our population we did not find a worse reperfusion rate in this patient group treated with IV-rtPA. [38] Another reason could be a difference in population characteristics between treated and non-treated patients, with a higher admission NIHSS in the IV-rtPA treated patients.

Although some predictors of reperfusion (size infarct core, size total ischemic area) have not been related to recanalization, most reperfusion predictors (NIHSS, clot burden score, thrombus location, collateral score) have been established for recanalization.[7, 16, 24, 32, 39-45] In addition several papers, describing predictors of reperfusion or recanalization showed a good correlation between these predictive factors and outcome (final infarct size and modified Rankin Score at 3 months).[6, 11, 16] This is not surprising, as reperfusion is a parameter situated between recanalization and outcome. Our data confirm that these relations are already established at day 3, relatively early in the clinical course. This suggests that follow-up reperfusion data could be used as a surrogate end point.

There are some limitations to this study. First, our patient group is seemingly different from those in many previous stroke papers because of shorter time to scan, lower NIHSS scores and higher IV-rtPA treatment rate. However, with improved stroke awareness and faster stroke protocols our population is probably more representative of the current stroke populations.

Second, the time to follow up was approximately 3 days. Most brain cells die early in ischemic conditions, but recanalization is known to continue even after the focal areas have infarcted. Timely and clinically meaningful recanalization and reperfusion may be better demonstrated when follow up is performed at an earlier time point.

Third, assessment of both recanalization and reperfusion was not done quantitatively but in a 2 point scale, a method also previously used.[46-48] The predictive value can improve

with more quantitative assessment but small lesions are prone to measurement errors.[15] Moreover, qualitative assessment is easier and shows good agreement in clinical practice, especially with limited lesion coverage.[49]

Fourth, the 26 patients with a peripheral perfusion deficit, who did not show an occlusion on the CTA, were included in the M2-MCA/distal occlusion group. It was assumed that the peripheral perfusion deficit in these patients was caused by a distal occlusion, not detectable on CTA. Possibly, some of these distal occlusions may have resulted from fragmentation of a larger thrombus and thus (partial) recanalization before the initial imaging. However, this seems unlikely as the median time to treatment in our study was only 100 minutes, which leaves little time for early recanalization to occur.



# Conclusions

This study confirms that recanalization and reperfusion outcomes in ischemic stroke are significantly related but not always interchangeable. Lower NIHSS, smaller size of the infarct core, smaller total ischemic area, lower clot burden, more distal intra-cranial thrombus location and good collateral scores, have been identified as predictors of complete reperfusion. A smaller total ischemic area is the only independent predictor of complete reperfusion.

# References


1. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC, Jr., Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363:768-774

2. Wintermark M, Albers GW, Broderick JP, Demchuk AM, Fiebach JB, Fiehler J, Grotta JC, Houser G, Jovin TG, Lees KR, Lev MH, Liebeskind DS, Luby M, Muir KW, Parsons MW, von Kummer R, Wardlaw JM, Wu O, Yoo AJ, Alexandrov AV, Alger JR, Aviv RI, Bammer R, Baron JC, Calamante F, Campbell BC, Carpenter TC, Christensen S, Copen WA, Derdeyn CP, Haley EC, Jr., Khatri P, Kudo K, Lansberg MG, Latour LL, Lee TY, Leigh R, Lin W, Lyden P, Mair G, Menon BK, Michel P, Mikulik R, Nogueira RG, Ostergaard L, Pedraza S, Riedel CH, Rowley HA, Sanelli PC, Sasaki M, Saver JL, Schaefer PW, Schellinger PD, Tsivgoulis G, Wechsler LR, White PM, Zaharchuk G, Zaidat OO, Davis SM, Donnan GA, Furlan AJ, Hacke W, Kang DW, Kidwell C, Thijs VN, Thomalla G, Warach SJ. Acute Stroke Imaging Research Roadmap II. Stroke. 2013;44:2628-2639

3. Dalkara T, Arsava EM. Can restoring incomplete microcirculatory reperfusion improve stroke outcome after thrombolysis? J Cereb Blood Flow Metab. 2012;32:2091-2099

4. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, Marks MP, Prabhakaran S, Kallmes DF, Fitzsimmons BF, Mocco J, Wardlaw JM, Barnwell SL, Jovin TG, Linfante I, Siddiqui AH, Alexander MJ, Hirsch JA, Wintermark M, Albers G, Woo HH, Heck DV, Lev M, Aviv R, Hacke W, Warach S, Broderick J, Derdeyn CP, Furlan A, Nogueira RG, Yavagal DR, Goyal M, Demchuk AM, Bendszus M, Liebeskind DS. Recommendations on Angiographic Revascularization Grading Standards for Acute Ischemic Stroke: A Consensus Statement. Stroke. 2013;44:2650-2663

5. Soares BP, Tong E, Hom J, Cheng SC, Bredno J, Boussel L, Smith WS, Wintermark M. Reperfusion is a more accurate predictor of follow-up infarct volume than recanalization: a proof of concept using CT in acute ischemic stroke patients. Stroke. 2010;41:e34-40

6. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol. 2006;60:508-517

7. Murphy A, Symons SP, Hopyan J, Aviv RI. Factors influencing clinically meaningful recanalization after IV-rtPA in acute ischemic stroke. AJNR Am J Neuroradiol. 2013;34:146-152

8. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. Stroke. 2006;37:1227-1231

9. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous

desmoteplase. Stroke. 2005;36:66-73

10. Fiehler J, Remmele C, Kucinski T, Rosenkranz M, Thomalla G, Weiller C, Zeumer H, Rother J. Reperfusion after severe local perfusion deficit precedes hemorrhagic transformation: an MRI study in acute stroke patients. Cerebrovasc Dis. 2005;19:117-124

11. Eilaghi A, Brooks J, d'Esterre C, Zhang L, Swartz RH, Lee TY, Aviv RI. Reperfusion Is a Stronger Predictor of Good Clinical Outcome than Recanalization in Ischemic Stroke. Radiology. 2013 Oct;269(1):240-8

12. De Silva DA, Fink JN, Christensen S, Ebinger M, Bladin C, Levi CR, Parsons M, Butcher K, Barber PA, Donnan GA, Davis SM. Assessing reperfusion and recanalization as markers of clinical outcomes after intravenous thrombolysis in the echoplanar imaging thrombolytic evaluation trial (EPITHET). Stroke. 2009;40:2872-2874

13. Yoo AJ. Revascularization Grading: The Devil Is in the Details. Radiology. 2013;269:6-7

14. Soares BP, Chien JD, Wintermark M. MR and CT monitoring of recanalization, reperfusion, and penumbra salvage: everything that recanalizes does not necessarily reperfuse! Stroke. 2009;40:S24-27

15. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7:299-309

16. Derex L, Nighoghossian N, Hermier M, Adeleine P, Berthezene Y, Philippeau F, Honnorat J, Froment JC, Trouillas P. Influence of pretreatment MRI parameters on clinical outcome, recanalization and infarct size in 49 stroke patients treated by intravenous tissue plasminogen activator. J Neurol Sci. 2004;225:3-9

17. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, O'Brien B, Bladin C, McElduff P, Allen C, Bateman G, Donnan G, Davis S, Levi C. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012;366:1099-1107

18. Ogata T, Christensen S, Nagakane Y, Ma H, Campbell BC, Churilov L, Lansberg MG, Straka M, De Silva DA, Mlynash M, Bammer R, Olivot JM, Desmond PM, Albers GW, Davis SM, Donnan GA. The effects of alteplase 3 to 6 hours after stroke in the EPITHET-DEFUSE combined dataset: post hoc case-control study. Stroke. 2013;44:87-93

19. Olivot JM, Mlynash M, Thijs VN, Purushotham A, Kemp S, Lansberg MG, Wechsler L, Gold GE, Bammer R, Marks MP, Albers GW. Geography, structure, and evolution of diffusion and perfusion lesions in Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE). Stroke. 2009;40:3245-3251

20. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke

trial (DUST) study protocol. BMC Neurol. 2014;14:37

21. 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. Lancet. 2000;355:1670-1674

22. Niesten JM, van der Schaaf IC, Riordan AJ, de Jong HW, Mali WP, Velthuis BK. Optimisation of vascular input and output functions in CT-perfusion imaging using 256(or more)-slice multidetector CT. Eur Radiol. 2013;23:1242-1249

23. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, Pineda C, Serena J, van der Schaaf I, Waaijer A, Anderson J, Nesbit G, Gabriely I, Medina V, Quiles A, Pohlman S, Quist M, Schnyder P, Bogousslavsky J, Dillon WP, Pedraza S. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37:979-985

24. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. AJNR Am J Neuroradiol. 2009;30:525-531

25. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61:533-543

26. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, O'Reilly C, Hudon ME, Hu WY, Coutts SB, Barber PA, Watson T, Roy J, Demchuk AM. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3:230-236

27. El-Mitwalli A, Saad M, Christou I, Malkoff M, Alexandrov AV. Clinical and sonographic patterns of tandem internal carotid artery/middle cerebral artery occlusion in tissue plasminogen activator-treated patients. Stroke. 2002;33:99-102

28. Molina CA, Alvarez-Sabin J. Recanalization and reperfusion therapies for acute ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl 1:162-167

29. del Zoppo GJ. Virchow's triad: the vascular basis of cerebral injury. Rev Neurol Dis. 2008;5 Suppl 1:S12-21

30. Wong CH, Crack PJ. Modulation of neuro-inflammation and vascular response by oxidative stress following cerebral ischemia-reperfusion injury. Curr Med Chem. 2008;15:1-14

31. Mendonca N, Rodriguez-Luna D, Rubiera M, Boned-Riera S, Ribo M, Pagola J, Pineiro S, Meler P, Alvarez-Sabin J, Montaner J, Molina CA. Predictors of tissue-type plasminogen activator nonresponders according to location of vessel occlusion. Stroke. 2012;43:417-421

32. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, Watson T, Goyal M, Demchuk AM. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. 2010;41:2254-2258

33. Yeo LL, Paliwal P, Teoh HL, Seet RC, Chan BP, Liang S, Venketasubramanian N, Rathakrishnan R, Ahmad A, Ng KW, Loh PK, Ong JJ, Wakerley BR, Chong VF, Bathla G, Sharma VK. Timing of recanalization after intravenous thrombolysis and functional outcomes after acute ischemic stroke. JAMA Neurol. 2013;70:353-358

34. Lemmens R, Mlynash M, Straka M, Kemp S, Bammer R, Marks MP, Albers GW, Lansberg MG. Comparison of the response to endovascular reperfusion in relation to site of arterial occlusion. Neurology. 2013;81:614-618

35. Kappelhof M, Marquering HA, Berkhemer OA, Majoie CB. Intra-arterial treatment of patients with acute ischemic stroke and internal carotid artery occlusion: a literature review. J Neurointerv Surg. 2014;Jan;7(1):8-15

36. Marks MP, Olivot JM, Kemp S, Lansberg MG, Bammer R, Wechsler LR, Albers GW, Thijs V. Patients with acute stroke treated with intravenous tPA 3-6 hours after stroke onset: correlations between MR angiography findings and perfusion- and diffusion-weighted imaging in the DEFUSE study. Radiology. 2008;249:614-623

37. Lansberg MG, Thijs VN, Bammer R, Olivot JM, Marks MP, Wechsler LR, Kemp S, Albers GW. The MRA-DWI mismatch identifies patients with stroke who are likely to benefit from reperfusion. Stroke. 2008;39:2491-2496

38. Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. AJNR Am J Neuroradiol. 2005;26:1789-1797

39. Shhadeh A, Garg A, Hassan AE, Hoover S, Saucedo S, Hassansad B, Cornett O, Tohidi V, Qureshi AI, Kirmani JF. Recanalization following various endovascular modalities for treatment of anterior circulation acute ischemic strokes. J Vasc Interv Neurol. 2012;5:10-16

40. Tandberg Askevold E, Naess H, Thomassen L. Predictors for recanalization after intravenous thrombolysis in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2007;16:21-24

41. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, Akhtar N, Orouk FO, Salam A, Shuaib A, Alexandrov AV. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007;38:948-954

42. Legrand L, Naggara O, Turc G, Mellerio C, Roca P, Calvet D, Labeyrie MA, Baron JC, Mas JL, Meder JF, Touze E, Oppenheim C. Clot burden score on admission T2*-MRI predicts recanalization in acute stroke. Stroke. 2013;44:1878-1884

43. Nam HS, Kim EY, Kim SH, Kim YD, Kim J, Lee HS, Nam CM, Heo JH. Prediction of thrombus resolution after intravenous thrombolysis assessed by CT-based thrombus imaging. Thromb Haemost. 2012;107:786-794

44. Zangerle A, Kiechl S, Spiegel M, Furtner M, Knoflach M, Werner P, Mair A, Wille G, Schmidauer C, Gautsch K, Gotwald T, Felber S, Poewe W, Willeit J. Recanalization after thrombolysis in stroke patients: predictors and prognostic implications. Neurology. 2007;68:39-44

45. Nambiar V, Sohn SI, Almekhlafi MA, Chang HW, Mishra S, Qazi E, Eesa M, Demchuk AM, Goyal M, Hill MD, Menon BK. CTA Collateral Status and Response to Recanalization in Patients with Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2013;May;35(5):884-90

46. Bivard A, Spratt N, Levi C, Parsons M. Perfusion computer tomography: imaging and clinical validation in acute ischaemic stroke. Brain. 2011;134:3408-3416

47. Kloska SP, Dittrich R, Fischer T, Nabavi DG, Fischbach R, Seidensticker P, Osada N, Ringelstein EB, Heindel W. Perfusion CT in acute stroke: prediction of vessel recanalization and clinical outcome in intravenous thrombolytic therapy. Eur Radiol. 2007;17:2491-2498

48. Olivot JM, Mlynash M, Thijs VN, Purushotham A, Kemp S, Lansberg MG, Wechsler L, Bammer R, Marks MP, Albers GW. Relationships between cerebral perfusion and reversibility of acute diffusion lesions in DEFUSE: insights from RADAR. Stroke. 2009;40:1692-1697

49. Luby M, Ku KD, Latour LL, Merino JG, Hsia AW, Lynch JK, Warach S. Visual perfusion-diffusion mismatch is equivalent to quantitative mismatch. Stroke. 2011;42:1010-1014

# CHAPTER 3

# Relation between stroke severity, patient characteristics and CT-perfusion derived blood-brain barrier permeability measurements in acute ischemic stroke

Alexander D. Horsch, Jan Willem Dankbaar, Tom van Seeters, Joris M. Niesten, Merel J.A. Luitse, Pieter C. Vos, Irene C. van der Schaaf, Geert-Jan Biessels, Yolanda van der Graaf, L. Jaap Kappelle, Willem P.Th.M. Mali, Birgitta K. Velthuis

Adapted from:
**Clin Neuroradiol; 2015: 25; Feb 27, 1-7**

# Abstract

## Background

Increased blood-brain barrier permeability (BBBP) can result from ischemia. In this study the relation between stroke severity, patient characteristics and admission BBBP values measured with CT-perfusion (CTP) was investigated in acute ischemic stroke patients.

## Methods

From prospective data of the Dutch acute stroke study 149 patients with a middle cerebral artery stroke and extended CTP were selected. BBBP values were measured in the penumbra and infarct core as defined by CTP thresholds, and in the contra-lateral hemisphere. The relation between stroke (severity) variables and patient characteristics, including early CT signs, dense vessel sign (DVS), time to scan and National Institute of Health Stroke Score (NIHSS), and BBBP parameters in penumbra and infarct core was quantified with regression analysis.

## Results

Early CT signs were related to higher BBBP values in the infarct core (B = 0.710), higher ipsi- to contra-lateral BBBP ratios (B = 0.326) and higher extraction ratios in the infarct core (B = 16.938). Females were found to have lower BBBP values in penumbra and infarct core (B = -0.446 and -0.776 respectively) and lower extraction ratios in the infarct core (B = -10.463). If a DVS was present the ipsi- to contra-lateral BBBP ratios were lower (B = -0.304). There was no relation between NIHSS or time to scan and BBBP values.

## Conclusion

Early CT signs are related to higher BBBP values in the infarct core, suggesting that only severe ischemic damage alters BBBP within the first hours after symptom onset.

# Introduction

Acute ischemic stroke induces damage to the blood-brain barrier (BBB).[1] Alterations in the BBB integrity related to stroke severity, duration of ischemia and reperfusion have been associated with development of hemorrhagic transformation (HT).[1-3] BBB permeability (BBBP) can be calculated from CT perfusion (CTP) data by obtaining an extended CTP acquisition and measuring progressive leakage of iodinated contrast out of the cerebral vessels.[4] As currently many stroke clinics routinely obtain CTP on admission in stroke patients, BBBP measurements with CTP could be a practical addition in prognostic and diagnostic stroke imaging.[5] To better understand the concept of permeability, thorough evaluation of BBBP measurements with CTP in stroke patients is required.



On arrival to the emergency department, the severity of stroke and ischemic damage differs considerably between patients. Since ischemia is thought to alter BBB integrity, BBBP is likely to be related to stroke severity at the time of CT scanning at admission. Furthermore, several factors intrinsic to the patient have been associated with increased BBBP. These factors include age, elevated diastolic pressure, increased glucose levels and atrial fibrillation.[3, 6-8] If BBBP measurements are an indicator of ischemic damage to the BBB there should be a relationship between these factors and CTP BBBP measurements at time of admission.

The purpose of this study was to evaluate the relationship between stroke severity, patient characteristics, and CTP BBB permeability values in a consecutive prospectively collected series of acute ischemic middle cerebral artery (MCA) stroke patients.

# Materials and methods

## Study design

In this study we used data from the Dutch acute stroke study (DUST). This is a large multicenter cohort study which aims to assess the additional value of CTP and CT angiography (CTA) in predicting outcome of acute ischemic stroke patients. Prospective inclusion was done between May 2009 and August 2013, and patients were enrolled in 14 DUST hospitals.[9]

Inclusion criteria for this study were: age ≥ 18 years, suspected ischemic stroke of less then 9 hours duration and National Institute of Health Stroke Scale (NIHSS) score of ≥2 (or 1 if an indication for thrombolysis was present). Exclusion criteria were known renal failure or contraindications to iodinated contrast material. This study was approved by the central ethics committee in the UMC Utrecht as well as the local institutional ethical review boards of the participating centers. All patients or family gave signed informed consent, unless a patient died before consent could be obtained. The need for consent in that case was waived by the medical ethics committee.[9] From this study database consecutive patients were selected

from 7 centers (Catharina Hospital Eindhoven, Leiden University Medical Center, Rijnstate Hospital Arnhem, St. Elizabeth Hospital Tilburg, St. Franciscus Hospital Rotterdam, University Medical Center Utrecht, VU Medical Center Amsterdam). We selected these centers from all DUST centers because of their respective start date of inclusion and availability of the data at the time of patient selection for this study.

Additional inclusion criteria for this study were: admission between May 2009 and July 2011 with a CTP deficit in the region of the middle cerebral artery and an extended CTP acquisition. Exclusion criteria were technical failure of the extended CTP (incomplete scan series, excessive movement or artifacts).



General baseline patient characteristics were collected on admission: age, sex, prior history of cardiovascular risk factors obtained by anamnesis (stroke, hypertension, diabetes, hyperlipidemia, angina, myocardial infarction), NIHSS, time from stroke onset to admission CT scan and blood glucose (mmol/l). Determinants were selected on the basis of prevalence in stroke population and potential influence on the integrity of the BBB.

## Imaging protocol

Non-contrast brain CT (NCCT), CTP with extended acquisition, and CTA of the cervical and cerebral vessel were performed on admission before possible thrombolytic treatment was initiated. Multi-detector CT scanners used were Philips iCT 256-detector, Philips 64-detector, Philips 40-detector, Toshiba 320-detector and Toshiba 64-detector. CT protocols were adjusted to scanner type and contrast agent used.

The CTP involved successive gantry rotations in cine mode during intra-venous administration of iodinated contrast material (40ml non-ionic contrast followed by 40ml of saline with a flow of 6ml/sec). Temporal sampling was obtained every 2 seconds for 50 seconds followed by six samples 30 seconds apart at 60, 90, 120, 150, 180 and 210 seconds. Only the Philips scanners required a separate scan to change the cycle time and the two separate scans were fused prior to permeability measurements. The Toshiba 320-detector scanner had full brain coverage. The other CT scanners had a coverage of 40-65mm (8 to thirteen 5mm slices) from at least the level of the basal ganglia to the lateral ventricles to be able to compare between patients.

Following CTP, a CTA was performed from aortic arch to the vertex with 50-70ml non-ionic contrast. The CTA data was not used for this study. All data and imaging processing was done centrally in Utrecht University Medical Center.

## Image post processing

Cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP) were automatically calculated from CTP data utilizing commercially available CTP software (Extended Brilliance workstation 4.5, Philips Healthcare). The internal carotid artery (if available in the scan range) or anterior cerebral artery was chosen as arterial input

function.[10] The superior saggital sinus was used as venous output function. A MTT threshold of 145% compared to non-affected side was used to define the ischemic area. Within this area a CBV value of less then 2.0 ml/100g was used to define the infarct core and a CBV of 2.0 ml/100g or more to define the penumbra.[5]

BBBP was calculated with a commercially available software based on the Patlak model (Intellispace Portal system, Philips Healthcare).[11] The Patlak model involves the fitting of a regression line to observations of time-density curves for each pixel and for intra-vascular reference function. The slope of these lines represents a local blood-to-brain transfer constant and is an indicator of BBBP values (perfusion derived permeability surface area product (PS) in ml/min/100g). To minimize the influence of larger size vessels, pixels with a CBV > 9 ml/100gram were removed. Circular regions of interest (ROIs) of identical size (100mm$^2$) were drawn in the center of the CTP threshold defined penumbra and infarct core and mirror-imaged ROIs were automatically drawn in the contra-lateral hemisphere (Figure 1). To correct for the potential influence of CBF, extraction ratio ((BBBP / CBF) x 100%) values were obtained in all four ROIs.[12, 13] All measurements were done blinded to other study data.

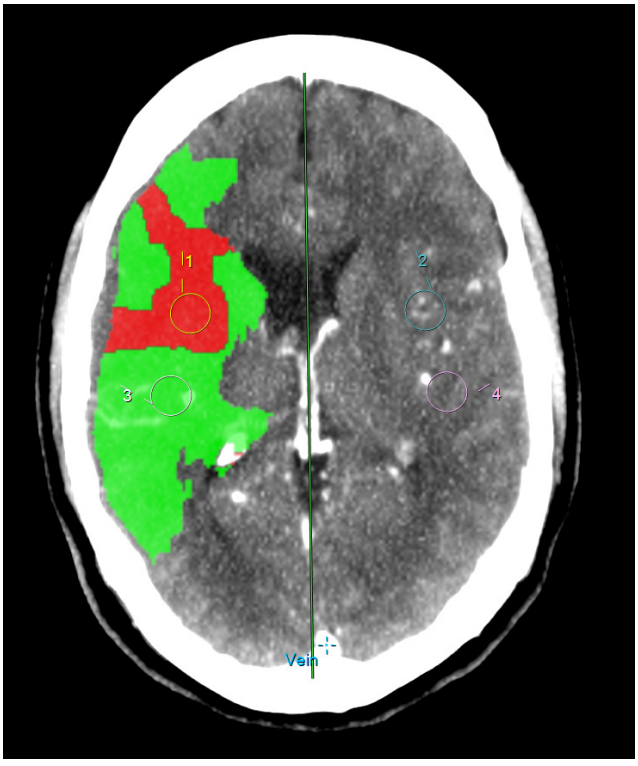



Figure. 1 Drawing of ROIs in infarct core and penumbra.

| Table 1. Patient, stroke and imaging characteristics. | |
|---|---|
| Number of patients | 149 |
| Age in years, median (IQ range) | 69 (59-80) |
| Sex, men % | 54 |
| **Patient characteristics** | |
| Cardiovascular risk factors, one or more of the following % | 71 |
| Angina % | 10 |
| Myocardial infarction % | 13 |
| Atrial fibrillation % | 13 |
| Diabetes % | 16 |
| Hyperlipidemia % | 30 |
| Hypertension % | 57 |
| Glucose in mmol/l, median (IQ range) | 7.1 (5.8-7.6) |
| **Stroke severity** | |
| NIHSS, mean (median, range) | 10 (8, 1-32) |
| Time from symptom onset to scan in hours, mean (median, range) | 3.0 (2.2 , 0.47 - 9) |
| 0-3 h % | 60 |
| 3-4.5 h % | 24 |
| 4.5-6 h % | 9 |
| 6-9 h % | 7 |
| **Imaging parameters** | |
| Dense vessel sign (DVS) % | 34 |
| Early CT signs (ECTS) % | 38 |
| Penumbra size in $cm^2$, median (IQ range) | 21 (6-40) |
| Infarct size in $cm^2$, median (IQ range) | 5 (1-17) |

### Image analysis

On the admission NCCT, the presence of early CT signs (ECTS), defined as hypodensity with or without swelling, and presence of a dense vessel sign (DVS) were evaluated by one of three observers (I.C.vdS, B.K.V and J.W.D), all with at least 5 years of experience in stroke imaging. The side of symptoms was provided but observers were blinded to other clinical and imaging data. Consensus was reached for all discrepant findings.

### Statistical analysis

Outcomes were BBBP in the penumbra- and infarct ROI and the contra-lateral hemisphere as well as BBBP ratios (ipsi-lateral/contra-lateral), and extraction ratio in both ROI's.[14] Variables referring to stroke severity were NIHSS (rearranged into quintiles), DVS, ECTS, and penumbra- and infarct size. Patient variables were age, sex, cardiovascular risk factors and glucose. Cardiovascular risk factors were dichotomized and considered positive if medical history included one of the following: hyperlipidemia, hypertension, diabetes, angina pectoris, myocardial infarction or atrial fibrillation. Prior to analysis outcome data were truncated to 5-95% to adjust for outliers. Statistical computations were carried out using SPSS 19.0 (IBM corporation, NY, USA). The relation between the determinants and permeability values was quantified with regression analysis. In the multivariate analysis all variables were initially included and then sequentially removed with a probability-to-enter of 0.05 until only significant predictors remained (p 0.10).



## Results

The inclusion criteria were met in 196 patients and 47 were subsequently excluded because of failed acquisition (22), motion artifacts (19) and beam hardening artifacts (6). Of the remaining 149 patients the stroke severity parameters and patient characteristics are summarized in Table 1.

Outcome values are shown in Table 2. The median permeability value in the ipsi-lateral penumbra was 1.89 and in the infarct core 1.74; contra-lateral values were 1.71 and 1.59 respectively. The median extraction ratio in the infarct core was 17% and 10% for the penumbra, and respectively 4% and 3% on the contra-lateral side, with a wide distribution. The median ratio of BBBP values between the ipsi-lateral and the mirrored contra-lateral area was 0.97 for the infarct core and 1.14 in the penumbra.

Univariate analysis (Table 3) showed significantly higher BBBP values in the infarct core (B = 0.276) in the presence of ECTS but not in the penumbra or contra-lateral ROIs. ECTS (B = 18.7) and infarct size (B = 0.463) were also related to higher extraction ratio in the infarct core. Additionally, lower permeability values in penumbra (B = -0.495) and infarct core (B =

**Table 2. Median BBB Permeability measurements.**

| | Ipsi-lateral (IQ range) | Contra-lateral (IQ range) | P-value |
|---|---|---|---|
| **BBB Permeability (in ml/100gr/min)** | | | |
| Penumbra | 1.89 (1.23-2.79) | 1.71 (1.15-2.73) | 0.3 |
| Infarct core | 1.74 (0.90-2.99) | 1.59 (1.03-2.59) | 0.6 |
| **Extraction ratio (BBB Permeability / CBF *100%)** | | | |
| Penumbra | 10.1 (5.65-16.76) | 3.2 (2.16-6.18) | * |
| Infarct core | 16.7 (9.38-33.26) | 4.1 (2.21-7.57) | * |
| **Ratio BBB Permeability ipsi-lateral / contra-lateral** | | | |
| Penumbra | 1.1 (0.79-1.61) | | N/A |
| Infarct core | 1.0 (0.67-1.53) | | N/A |
| **Ratio BBB Permeability ipsi-lateral / contra-lateral** | | | |
| Penumbra | 1.1 (0.79-1.61) | | N/A |
| Infarct core | 1.0 (0.67-1.53) | | N/A |

* Mann-Whitney U test not performed due to large difference in range between samples.

-0.786) were found in female patients. All other parameters, including dense vessel sign, did not show significantly higher or lower BBBP values.

In multivariate analysis (Table 4) ECTS were related to higher BBBP values in the infarct core (B = 0.710), higher ipsi- to contra-lateral BBBP ratios (B = 0.326) and higher extraction ratios in the infarct core (B = 16.938). Females showed lower BBBP values in penumbra and infarct core (B = -0.446 and -0.776 respectively) and lower extraction ratios in the infarct core (B = -10.463). If a DVS is present the ipsi- to contra-lateral BBBP ratios in the infarct core were lower (B = -0.304).

**Table 3. Univariate analysis of the relation between stroke severity, patient characteristics and BBB Permeability values.**

| | BBB Permeability penumbra | | BBB Permeability infarct core | | Extraction ratio infarct core | | BBB Permeability ratio infarct core | |
|---|---|---|---|---|---|---|---|---|
| **Predictor:** | **B** | **95% CI** | **B** | **95% CI** | **B** | **95% CI** | **B** | **95% CI** |
| Age (in years) | -0.008 | -0.026 to 0.010 | -0.020 | -0.042 to 0.003 | -0.197 | -0.633 to 0.238 | -0.006 | -0.018 to 0.006 |
| Female sex | -0.495* | -0.958 to -0.032 | -0.786* | -1.386 to -0.186 | -11.251 | -22.540 to 0.038 | -0.097 | -0.428 to 0.235 |
| NIHSS [1] | -0.043 | -0.217 to 0.131 | -0.007 | -0.238 to 0.223 | 2.200 | -2.032 to 6.432 | -0.081 | -0.204 to 0.042 |
| Time to scan [2] | 0.008 | -0.097 to 0.112 | 0.049 | -0.090 to 0.188 | -0.260 | -2.794 to 2.273 | 0.013 | -0.062 to 0.087 |
| Cardiovascular risk factors (yes/no) [3] | 0.222 | -0.280 to 0.725 | -0.065 | -0.726 to 0.596 | 2.731 | -9.550 to 15.012 | 0.167 | -0.189 to 0.523 |
| Glucose (mmol/l) | 0.064 | -0.083 to 0.212 | 0.012 | -0.180 to 0.204 | 2.247 | -1.122 to 5.616 | -0.019 | -0.124 to 0.085 |
| Dense vessel sign (yes/no) | 0.134 | -0.360 to 0.629 | 0.374 | -0.256 to 1.004 | 7.213 | -4.742 to 19.167 | -0.188 | -0.526 to 0.151 |
| Early CT signs (yes/no) | 0.232 | -0.247 to 0.712 | 0.819* | 0.214 to 1.424 | 18.709* | 7.397 to 30.020 | 0.276 | -0.055 to 0.607 |
| Penumbra size ($cm^2$) | 0.003 | -0.009 to 0.015 | 0.010 | -0.005 to 0.026 | 0.228 | -0.063 to 0.520 | -0.005 | -0.013 to 0.004 |
| Infarct size ($cm^2$) | -0.003 | -0.020 to 0.013 | 0.007 | -0.014 to 0.029 | 0.463* | 0.062 to 0.864 | -0.003 | -0.014 to 0.009 |

* P<0.05,
[1] In 5 categories: 1-3, 4-6, 7-12, 13-17 and 18 or higher,
[2] In 4 categories: 0-3, 3-4,5 4.5-6 and 6-9 hours,
[3] Any from: hyperlipidemia, hypertension, diabetes, angina pectoris, myocardial infarction or atrial fibrillation

**Table 4. Multivariate analysis of the relation between stroke severity, patient characteristics and BBB Permeability values.**

| BBB Permeability penumbra | | | BBB Permeability infarct core | | | Extraction ratio infarct core | | | BBB Permeability ratio infarct core | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Predictor | B | 95% CI | Predictor | B | 95% CI | Predictor | B | 95% CI | Predictor | B | 95% CI |
| Female sex | -0.446 | -0.909 to 0.016 | Female sex | -0.776 | -1.358 to -0.194 | Female sex | -10.463 | -20.665 to -0.271 | | | |
| | | | Early CT signs | 0.710 | 0.120 to 1.300 | Early CT signs | 16.938 | 6.449 to 27.427 | Early CT signs | 0.326 | -0.026 to 0.679 |
| | | | | | | | | | Dense vessel sign (DVS) | -0.304 | -0.660 to 0.053 |

All P<0.10

# Discussion

The most important finding in this study is that only ECTS are related to higher permeability values in the infarct core on admission, when calculated using the Patlak model. No significant differences were found between median BBBP values in the penumbra, infarct core and the unaffected contra-lateral hemisphere.

Median infarct BBBP values in our study fall in the range of previously published values (0.34 to 3.5 ml/100g/min).[15-18] Median penumbra BBBP values have only been published in one study with a value of 2.48 ml/100gr/min, which was higher than the value found in this study.[19] Unfortunately, we could not find any significant difference between values calculated in the different brain tissue types. Also, the ratio of permeability in the infarct core and the penumbra compared to the contra-lateral side was close to 1, and measured permeability values were similar in both hemispheres. This raises serious concerns about the applied technique. The finding that BBBP calculated with the Patlak model is not zero in the unaffected hemisphere suggests that a large level of noise influences the measurement of permeability in the used CTP acquisitions. The absence of differences between the different tissue types implies that the signal from the leaked contrast is not large enough to overcome the level of noise. Advanced noise filtering may be a solution to these problems.[20] The lack of signal will most likely be largest in an area of least flow, since hardly any contrast enters the tissue and can therefore not leak out. Our intention to overcome this issue by calculating the extraction ratio did result in more obvious differences between the tissue types, however with a very wide distribution.

In our multivariate analysis of factors describing stroke severity on BBBP only ECTS showed a positive relationship with higher BBBP values. Since ECTS are a sign of severe and often irreversible ischemia, our findings suggest that only severe ischemia induces measurable BBB breakdown within the first hours after acute ischemic stroke.[21, 22] The size of the ischemic defect does not seem to influence BBBP values, as there is no significant relationship with infarct core or penumbra size. It still needs to be evaluated whether BBBP is a better predictor of HT in comparison to ECTS.

The lower ipsi-lateral to contra-lateral ratios of BBBP found in the infarct core when a dense vessel sign is present is difficult to explain as we expected higher values instead of lower values. A DVS has a high specificity and positive predictive value for diagnosing acute occlusion of the M1 segment of the MCA.[23, 24] In some articles a DVS in the MCA is associated with more severe neurologic deficit at presentation, more extensive area of brain infarction, and worse neurologic outcome after thrombolysis.[23-25] In contrast, other studies found no relation between DVS and poor outcome.[26-29] A possible explanation for the lower values in this study are that hyperdense MCA sign (M1 segment) and MCA dot sign (M2 or higher) were grouped together although the prognosis of a M2 segment MCA occlusion was found to be better

by Barber et al. 2001.[30] Secondly, DVS is related to local vessel occlusion but this does not necessarily lead to tissue hypo-perfusion if distal collaterals provide sufficient perfusion.

Of the factors describing patient characteristics only female gender was associated with lower BBBP values. There are clear gender differences in acute ischemic stroke and estrogens and pro-inflammatory cytokine production during cerebral ischemia are thought to be related to these differences.[31, 32] The relationship between female sex and reduced disruption of the BBB has been found in several animal studies but so far could not be confirmed in human studies.[19, 33-36] Our study with human subjects does confirm that some relation between female sex and BBB integrity in acute ischemic stroke exists, but further studies are still needed to clarify this issue. In contrast to Bang et al. 2009, age and NIHSS were not related to significant differences in permeability values.[6]



Besides the low signal-to-noise ratio of the BBBP measurements with the Patlak model from CTP data we acknowledge several other limitations to our study. First, we had to exclude nearly 25% of patients due to technical failure of the CTP. Compared to the numbers found in other studies our percentage is rather high. The technical failure was largely related to the extended acquisition necessary to calculate BBBP with the Patlak model.[4, 17] At present, not all CT vendors can change the cycle time from the initial two-second cycle time to the 30 second extended cycle time. This requires two separate perfusion scans which can cause difficulty in merging the two datasets for analysis. In addition, extending the acquisition time from 50 to 210 seconds also increases the risk of motion artefacts, which are especially difficult to correct in the z-direction. Second, we only used the Patlak model in this study which assumes unidirectional transfer without backflow and requires steady state contrast levels. This assumption is possibly not sufficiently accurate and technical improvement with other models (e.g. distributed parameter model) needs to be tested. The first results of such a model have been published recently.[37] Measurable BBBP values above the noise level are prerequisite to be able to predict possible hemorrhagic transformation. Third, no gold standard for the definition of infarct core and penumbra with CTP has been established so far. It is possible that when using other thresholds described in literature, the ROI's would have been different, resulting in other permeability values that might have correlated differently with BBBP. However, the definition of infarct core and penumbra we used has frequently been applied in literature and is the default setting in the post-processing software we used. This makes our results more reproducible for general stroke work-up when this software is used.

# Conclusions

BBB permeability assessment with the Patlak model from CTP acquisition in stroke patients is technically challenging and limited by the current signal-to-noise ratio. In this study we found higher BBBP measurements when early ischemic changes on admission NCCT are

present. This suggests that severe ischemic damage results in measurable BBBP alterations within the first hours after symptom onset.

# References


1. Sandoval KE, Witt KA. Blood-brain barrier tight junction permeability and ischemic stroke. Neurobiol Dis. 2008;32:200-219

2. Aviv RI, d'Esterre CD, Murphy BD, Hopyan JJ, Buck B, Mallia G, Li V, Zhang L, Symons SP, Lee TY. Hemorrhagic transformation of ischemic stroke: prediction with CT perfusion. Radiology. 2009;250:867-877

3. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, Lau BC, Smith W, Dillon WP, Wintermark M. Blood-Brain Barrier Permeability Assessed by Perfusion CT Predicts Symptomatic Hemorrhagic Transformation and Malignant Edema in Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2011;32:41-48

4. Hom J, Dankbaar JW, Schneider T, Cheng SC, Bredno J, Wintermark M. Optimal Duration of Acquisition for Dynamic Perfusion CT Assessment of Blood-Brain Barrier Permeability Using the Patlak Model. AJNR Am J Neuroradiol. 2009;30:1366-1370

5. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, Pineda C, Serena J, van der Schaaf I, Waaijer A, Anderson J, Nesbit G, Gabriely I, Medina V, Quiles A, Pohlman S, Quist M, Schnyder P, Bogousslavsky J, Dillon WP, Pedraza S. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37:979-985

6. Bang OY, Saver JL, Alger JR, Shah SH, Buck BH, Starkman S, Ovbiagele B, Liebeskind DS. Patterns and Predictors of Blood-Brain Barrier Permeability Derangements in Acute Ischemic Stroke. Stroke. 2009;40:454-461

7. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease--systematic review and meta-analysis. Neurobiol Aging. 2009;30:337-352

8. Starr JM, Wardlaw J, Ferguson K, MacLullich A, Deary IJ, Marshall I. Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2003;74:70-76

9. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37

10. Niesten JM, van der Schaaf IC, Riordan AJ, de Jong HW, Mali WP, Velthuis BK. Optimisation of vascular input and output functions in CT-perfusion imaging using 256(or more)-slice multidetector CT. Eur Radiol. 2013;23:1242-1249

11. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab. 1983;3:1-7

12. Bisdas S, Hartel M, Cheong LH, Koh TS, Vogl TJ. Prediction of subsequent hemorrhage in acute ischemic stroke using permeability CT imaging and a distributed parameter tracer kinetic model.

J Neuroradiol. 2007;34:101-108

13. Dankbaar JW, Hom J, Schneider T, Cheng SC, Lau BC, van der Schaaf I, Virmani S, Pohlman S, Wintermark M. Age- and anatomy-related values of blood-brain barrier permeability measured by perfusion-CT in non-stroke patients. J Neuroradiol. 2009;36:219-227

14. Dankbaar JW, Rijsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology. 2009;51:813-819

15. Thornhill RE, Chen S, Rammo W, Mikulis DJ, Kassner A. Contrast-Enhanced MR Imaging in Acute Ischemic Stroke: T2* Measures of Blood-Brain Barrier Permeability and Their Relationship to T1 Estimates and Hemorrhagic Transformation. AJNR Am J Neuroradiol. 2010;31:1015-1022

16. Wu S, Thornhill RE, Chen S, Rammo W, Mikulis DJ, Kassner A. Relative recirculation: a fast, model-free surrogate for the measurement of blood-brain barrier permeability and the prediction of hemorrhagic transformation in acute ischemic stroke. Invest Radiol. 2009;44:662-668

17. Vidarsson L, Thornhill RE, Liu F, Mikulis DJ, Kassner A. Quantitative permeability magnetic resonance imaging in acute ischemic stroke: how long do we need to scan? Magn Reson Imaging. 2009;27:1216-1222

18. Kassner A, Roberts TPL, Moran B, Silver FL, Mikulis DJ. Recombinant Tissue Plasminogen Activator Increases Blood-Brain Barrier Disruption in Acute Ischemic Stroke: An MR Imaging Permeability Study. AJNR Am J Neuroradiol. 2009;30:1864-1869

19. Dankbaar JW, Hom J, Schneider T, Cheng SC, Bredno J, Lau BC, van der Schaaf IC, Wintermark M. Dynamic perfusion-CT assessment of early changes in blood brain barrier permeability of acute ischaemic stroke patients. J Neuroradiol. 2011;38:161-166

20. Mendrik AM, Vonken EJ, van Ginneken B, de Jong HW, Riordan A, van Seeters T, Smit EJ, Viergever MA, Prokop M. TIPS bilateral noise reduction in 4D CT perfusion scans produces high-quality cerebral blood flow maps. Phys Med Biol. 2011;56:3857-3872

21. von Kummer R, Bourquain H, Bastianello S, Bozzao L, Manelfe C, Meier D, Hacke W. Early prediction of irreversible brain damage after ischemic stroke at CT. Radiology. 2001;219:95-100

22. Somford DM, Marks MP, Thijs VN, Tong DC. Association of early CT abnormalities, infarct size, and apparent diffusion coefficient reduction in acute ischemic stroke. AJNR Am J Neuroradiol. 2004;25:933-938

23. Bastianello S, Pierallini A, Colonnese C, Brughitta G, Angeloni U, Antonelli M, Fantozzi LM, Fieschi C, Bozzao L. Hyperdense middle cerebral artery CT sign. Comparison with angiography in the acute phase of ischemic supratentorial infarction. Neuroradiology. 1991;33:207-211

24. Mattle HP, Arnold M, Georgiadis D, Baumann C, Nedeltchev K, Benninger D, Remonda L, von Budingen C, Diana A, Pangalu A, Schroth G, Baumgartner RW. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. Stroke. 2008;39:379-383

25. Agarwal P, Kumar S, Hariharan S, Eshkar N, Verro P, Cohen B, Sen S. Hyperdense middle cerebral artery sign: can it be used to select intra-arterial versus intravenous thrombolysis in acute ischemic stroke? Cerebrovasc Dis. 2004;17:182-190

26. Leys D, Pruvo JP, Godefroy O, Rondepierre P, Leclerc X. Prevalence and significance of hyperdense middle cerebral artery in acute stroke. Stroke. 1992;23:317-324

27. Tomsick T, Brott T, Barsan W, Broderick J, Haley EC, Spilker J, Khoury J. Prognostic value of the hyperdense middle cerebral artery sign and stroke scale score before ultraearly thrombolytic therapy. AJNR Am J Neuroradiol. 1996;17:79-85

28. Rauch RA, Bazan C, 3rd, Larsson EM, Jinkins JR. Hyperdense middle cerebral arteries identified on CT as a false sign of vascular occlusion. AJNR Am J Neuroradiol. 1993;14:669-673

29. Roberts HC, Dillon WP, Furlan AJ, Wechsler LR, Rowley HA, Fischbein NJ, Higashida RT, Kase C, Schulz GA, Lu Y, Firszt CM. Computed tomographic findings in patients undergoing intra-arterial thrombolysis for acute ischemic stroke due to middle cerebral artery occlusion: results from the PROACT II trial. Stroke. 2002;33:1557-1565

30. Barber PA, Demchuk AM, Hudon ME, Pexman JH, Hill MD, Buchan AM. Hyperdense sylvian fissure MCA "dot" sign: A CT marker of acute ischemia. Stroke. 2001;32:84-88

31. Czlonkowska A, Ciesielska A, Gromadzka G, Kurkowska-Jastrzebska I. Gender differences in neurological disease: role of estrogens and cytokines. Endocrine. 2006;29:243-256

32. Madsen TE, Seigel TA, Mackenzie RS, Marcolini EG, Wira CR, Healy ME, Wright DW, Gentile NT. Gender differences in neurologic emergencies part I: a consensus summary and research agenda on cerebrovascular disease. Acad Emerg Med. 2014;21:1403-1413

33. Semenas E, Sharma HS, Nozari A, Basu S, Wiklund L. Neuroprotective effects of 17beta-estradiol after hypovolemic cardiac arrest in immature piglets: the role of nitric oxide and peroxidation. Shock. 2011;36:30-37

34. Anishchenko TG, Brill GE, Romanova TP, Igosheva NB. Sex differences in adrenocortical sensitivity and resistance to cerebrovascular damage in rats under strong stress. Biull Eksp Biol Med. 1992;114:353-355

35. Sirav B, Seyhan N. Blood-brain barrier disruption by continuous-wave radio frequency radiation. Electromagn Biol Med. 2009;28:215-222

36. Oztas B, Akgul S, Seker FB. Gender difference in the influence of antioxidants on the blood-brain barrier permeability during pentylenetetrazol-induced seizures in hyperthermic rat pups. Biol Trace Elem Res. 2007;118:77-83

37. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751

# CHAPTER 4

# Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke

Alexander D. Horsch, Jan Willem Dankbaar, Yolanda van der Graaf, Joris M. Niesten, Tom van Seeters, Irene C. van der Schaaf, L. Jaap Kappelle, Birgitta K. Velthuis, on behalf of the DUST investigators

Adapted from:
**Neuroradiology (2015) 57:1219–1225**

# Abstract

## Background

Intra-venous recombinant tissue Plasminogen Activator (IV-rtPA) is given in acute ischemic stroke patients to achieve reperfusion. Hemorrhagic transformation (HT) is a serious complication of IV-rtPA treatment and related to blood-brain barrier (BBB) injury. It is unclear whether HT occurs secondary to reperfusion in combination with ischemic BBB injury or is caused by the negative effect of IV-rtPA on BBB integrity. The aim of this study was to establish the association between reperfusion and the occurrence of HT.

## Methods

From the Dutch acute stroke study (DUST) patients were selected with admission and follow-up non-contrast CT (NCCT) and CT perfusion (CTP) imaging, and a perfusion deficit in the middle cerebral artery territory on admission. Reperfusion was categorized qualitatively as reperfusion or no-reperfusion by visual comparison of admission and follow-up CTP. Occurrence of HT was assessed on follow-up NCCT. The association between reperfusion and occurrence of HT on follow-up was estimated by calculating odds ratios (OR) and 95% confidence intervals (CI) with additional stratification for IV-rtPA treatment.

## Results

Inclusion criteria were met in 299 patients. There was no significant association between reperfusion and HT (OR 1.2 95% CI 0.5-3.1). In patients treated with IV-rtPA (n=203) the OR was 1.3 (95% CI 0.4-4.0) and in patients not treated with IV-rtPA (n=96) the OR was 0.8 (95% CI 0.1-4.5). HT occurred in 14% of the IV-rtPA patients and in 7% of patients without IV-rtPA (95% CI of difference -1-14%).

## Conclusion

Our results suggest that the increased risk of HT after acute ischemic stroke treatment is not dependent on the reperfusion status.

# Introduction

Timely restoration of the downstream capillary blood flow (reperfusion) by recanalization of the occluded vessel in acute ischemic stroke patients is associated with favorable clinical outcome.[1, 2] However, reperfusion has also been associated with the occurrence of hemorrhagic transformation (HT) through a mechanism called reperfusion injury.[1, 3-5] HT incorporates all types of post-ischemic hemorrhages, ranging from the smaller hemorrhagic infarction (HI) type-1 or type-2, to the larger parenchymal hemorrhage (PH) type-1 or type-2. Especially the PH types may increase the risk of worse clinical outcome.[6-9] To induce reperfusion and thereby improve clinical outcome intra-venous recombinant tissue Plasminogen Activator (IV-rtPA) can be given within 4.5 hours after symptom onset.[10] However, IV-rtPA also increases the risk of HT by its thrombolytic action as well as by causing direct damage to the blood brain barrier (BBB).[10-13] It is unclear whether HT after ischemic stroke is caused mainly by reperfusion of an ischemic area with damage to the BBB or by the detrimental effects of IV-rtPA on the BBB.[3, 9] To further explore this topic, first the relation between reperfusion and the occurrence of HT needs to be investigated.

The purpose of this study was to investigate the association between reperfusion and the occurrence of HT, both in patients treated with and without IV-rtPA.



# Materials and methods

## Study design

The Dutch acute stroke study (DUST) is a large prospective multicenter cohort study that aims to assess the value of CT perfusion (CTP) and CT angiography (CTA) in addition to patient characteristics and non-contrast CT (NCCT) for prediction of outcome in patients with acute ischemic stroke (ClinicalTrials.gov NCT00880113). Patients were included in 14 hospitals between May 2009 and August 2013.[14]

Inclusion criteria for the DUST were: age > 18 years, suspected ischemic stroke of less then 9 hours duration and National Institutes of Health Stroke Scale (NIHSS) ≥2, or 1 if an indication for IV-rtPA was present. Exclusion criteria were known renal failure, contraindications for iodinated contrast material, and hemorrhage or another diagnosis seen on NCCT to explain the stroke symptoms. This study was approved by the central ethics committee in the UMC Utrecht and the local institutional ethical review boards of the participating hospitals. Patients or family gave signed informed consent unless a patient died before consent could be obtained, in which case the need for consent was waived by the medical ethics committee.[14]

## Patient selection

From the prospectively collected DUST database patients were retrospectively selected with (1) admission and follow-up NCCT and CT perfusion and (2) a perfusion deficit in the middle cerebral artery territory on admission CTP. Exclusion criteria were: (1) intra-arterial treatment, (2) poor quality CTP or (3) absence of one of the Alberta Stroke Program Early CT Score (ASPECTS) levels on CTP. The inclusion process is clarified in the flow chart (Figure 1). Collected clinical data were age, sex, history of stroke or hypertension, NIHSS on admission, IV-rtPA treatment and time from symptom onset to admission CT scan series.

## Imaging protocol and post-processing

In all DUST patients NCCT, CTP and CTA were performed on admission. Non-obligatory follow-up NCCT was planned after 3 days (+/- 2 days) and also performed in case of clinical deterioration. Additional follow-up CTA and CTP were performed if possible. For the current study patients were included only if follow-up imaging was performed with NCCT and CTP. All imaging studies were performed on multi-detector CT scanners ranging from 40 to 320 detectors. The CT protocol has been described previously.[14]

In short, the CTP involved successive gantry rotations in cine mode during intra-venous administration of iodinated contrast material (40ml non-ionic contrast) followed by 40ml of saline, both with a flow of 6ml/s. The CTP covered at least the level of the basal ganglia to the lateral ventricles to be able to assess ASPECTS levels 1 and 2, and compare between scanners with different number of detectors.[15]

From the acquired CTP data color-maps were created for cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP) utilizing commercially available CTP software (Extended Brilliance workstation 4.5, Philips

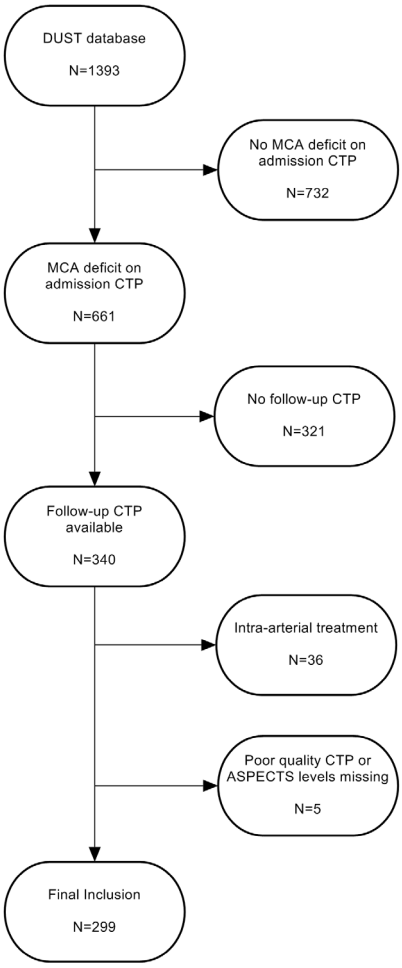



Figure 1. Flow chart patient selection

Healthcare). This software uses a deconvolution-based method which determines the MTT by the difference in first moment of tissue and arterial time attenuation curves.[16, 17] To calculate the CBF from the MTT, the software applies the central volume principle which is the most accurate for low injection rates of iodinated contrast material.[18] The internal carotid artery (if available in the scan range) or anterior cerebral artery was chosen as arterial input function.[19] The superior sagittal sinus was used as venous output function.

All data and imaging processing was done centrally in the UMC Utrecht. Scans were evaluated by one of three observers with more than 5 years of stroke imaging experience (B.K.V., I.C.vd.S, J.W.D.). The side of symptoms was provided but observers were blinded to other clinical and imaging data. Consensus was reached for ambiguous findings by an extra review by two of the three radiologists, also blinded to other clinical and imaging data. The number of consensus agreement cases was not collected.



## Reperfusion

Presence of reperfusion status was analyzed by visual comparison of the size of the perfusion abnormality on admission and follow-up CTP maps for cerebral blood volume, cerebral blood flow, mean transit time and time to peak. Reperfusion was classified qualitatively in a reperfusion and a no-reperfusion group. No-reperfusion was defined as the absence of any visually apparent change in the size of the perfusion deficit on follow-up CTP compared to the admission CTP. Partial reperfusion and hyperperfusion were included in the reperfusion group and an enlarged or new perfusion deficit in the no-reperfusion group.

## Hemorrhagic transformation

The follow-up NCCT was evaluated for the presence of hemorrhage. Hemorrhages were classified according to the European Cooperative Acute Stroke Study-1 (ECASS-1) criteria: HI-1 (small petechiae along the margins of infarct), HI-2 (confluent petechiae within infarcted area but no space-occupying effect), PH-1 (blood clots in 30% or less of the infarcted area with some slight space-occupying effect) and PH-2 (blood clots of more than 30% of infarcted area with substantial space-occupying effect).[7, 20]

## Statistical analysis

Patient characteristics were presented as number and percentages, mean and standard deviation (SD) or median and inter-quartile range (IQ). Differences between patients with and without IV-rtPA treated were tested with the chi-squared test to compare categorical variables and the Mann–Whitney U test for continuous variables.

The primary outcome was occurrence of any HT (all ECASS categories together). We estimated the association between reperfusion and the occurrence of HT by calculating odds ratios with 95% confidence intervals (95% CI) in the total group of patients and in the subgroups with and without IV-rtPA treatment.

**Table 1. Baseline clinical and imaging characteristics.**

| | All patients N=299 | rtPA N=203 (68%) | no rtPA N=96 (32%) | P-value |
|---|---|---|---|---|
| **Clinical parameters** | | | | |
| Age, median (IQ) | 68 (58-77) | 68 (56-75) | 70 (61-78) | 0.10 |
| Female sex, n (% ) | 116 (39) | 79 (39) | 37 (39) | 0.95 |
| Prior stroke, n (% ) | 68 (23) | 35 (17) | 33 (34) | 0.001* |
| Hypertension, n (% ) | 154 (52) | 95 (47) | 59 (62) | 0.02* |
| NIHSS, median (IQ) | 8 (5-14) | 9 (6-15) | 6 (3-12) | 0.002* |
| **Imaging parameters** | | | | |
| Time to admission scan, minutes, median (IQ) | 103 (65-163) | 84 (60-133) | 218 (133-315) | 0.006* |
| **Non-contrast CT** | | | | |
| HT, n (%) | 36 (12) | 29 (14) | 7 (7) | 0.08 |
| **CT perfusion** | | | | |
| No reperfusion, n (%) | 58 (19) | 34 (17) | 24 (25) | 0.09 |

Chi-squared test was used to compare categorical variables and Mann–Whitney U test for continuous variables
CTP, CT perfusion; HT, hemorrhagic transformation; IQ, interquartile range; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue Plasminogen Activator.
* $p<0.05$

# Results

From the DUST database of 1393 patients with complete admission data, 299 patients met inclusion criteria for this study. A total of 36 HT (12%) occurred in this selected patient group (ECASS HI-1: 13, HI-2: 15, PH-1: 7 and PH-2: 1). The overall percentage was comparable to the percentage of HT in the whole DUST database (11%). The main reasons for exclusion was the absence of an ischemic deficit on admission CTP (n=732) or because no follow-up CTP imaging was done (n=321). No significant difference was found in 3 months modified

Rankin Score between included and all excluded patients.

Clinical and imaging characteristics are summarized in Table 1. Treatment with IV-rtPA was given in 203 of the 299 patients (68%). Patients treated with IV-rtPA less often had a prior history of stroke or hypertension, had a significantly higher median NIHSS on admission (9 versus 6) and had a shorter median time to scan than patients who did not receive IV-rtPA (84 versus 218 minutes).

Reperfusion (median assessed at day 3) was visible in 241 patients (81%). There was no significant association between HT and reperfusion status in all patients (OR 1.2 95% CI 0.5-3.1). Of the 36 (12%) patients with HT, 29 received IV-rtPA treatment and 7 did not. HT occurred twice as often in patients treated with IV-rtPA compared to patients not treated with IV-rtPA (14% versus 7% with a 95% CI -1-14% for the difference). Both in patients treated with IV-rtPA and in patients not treated with IV-rtPA there was no significant association between reperfusion and HT (OR 1.3 (95% CI 0.4-4.0) and OR 0.8 (95% CI 0.1-4.5) respectively).



The results of a sub-analysis show that of the 28 patients with HI type hemorrhages, 25 (89%) showed reperfusion, while 3 (21%) did not. Of the 8 patients with PH type hemorrhage, 5 (63%) showed reperfusion while 3 (37%) did not.

# Discussion

The main finding in this study is that the overall occurrence of hemorrhagic transformation 3 days after onset of acute ischemic stroke does not seem to be associated with reperfusion.

Our findings are in contradiction to Fiehler et al. 2005 who suggested, in a retrospective MRI study in which HT occurred in 19 of the 51 patients, that HT in patients treated with IV-rtPA might be caused by a higher incidence of local reperfusion in the HT area.[3] However, in this study no significant difference in the occurrence of reperfusion between patients with and without HT could be shown if the entire admission perfusion abnormality area was considered. Moreover, the definition of reperfusion used in that study was only based on changes in TTP delay measured with MRI instead of CT, which could lead to differences in measuring the infarct core and penumbra and hence to different results.[3] Another retrospective MRI study, with HT occurring in 22 of the 144 patients, stated that reperfusion was the most significant independent predictor of early BBB disruption and that this BBB disruption was an independent predictor of HT.[21] However, they did not show a direct relation between reperfusion and HT. BBB disruption was defined as post gadolinium CSF enhancement, a technique not frequently used in clinical practice. Moreover, only 25% of their patients received IV-rtPA and no significant association between IV-rtPA and HT was shown.[21]

To our knowledge, our study is the largest prospectively collected dataset to evaluate the

association between reperfusion and HT. The overall percentage of HT patients in our study was within the range of previously published data on CT-follow-up literature.[12, 22] There was a clear difference in the occurrence of HT between patients treated with IV-rtPA and patients not treated with IV-rtPA, despite the absence of an association with reperfusion. This might be an indication that the delivery of rtPA to the ischemic area and not the reperfusion itself results in HT. However, other factors like stroke severity or time to treatment may also play a role.

Treatment with IV-rtPA was given in 68% of our patients. This percentage is much higher compared to other studies and possibly reflects the increased stroke awareness in The Netherlands and subsequent shorter time to admission. A selection bias in the DUST study with preference given to inclusion of patients eligible for IV-rtPA treatment could also be the reason for this higher percentage of treated patients.



The results of the sub-analysis of the HI type and PH type hemorrhages suggest that there is a trend towards a higher reperfusion rate in patients developing HI type hemorrhages, while PH type hemorrhages seem less related to reperfusion. This is in accordance with the findings of ECASS-2 which showed better outcomes with HI type hemorrhage and worse outcomes with PH type hemorrhages, possibly related to reperfusion status.[23] Unfortunately, the numbers in the sub-analysis are too low to perform meaningful statistical analysis on these subgroups. As we already derived our population from the whole DUST database, we were unable to test this in a larger cohort of patients.

Although we did not show a relation between reperfusion and the occurrence of hemorrhagic transformation, it is possible that this is due to the fact that the exact location of the hemorrhage is difficult to ascertain and that the reperfusion in a very focal area could be of importance. It could be argued that with the use of higher resolution thin sliced CTP and added filtering and noise reduction this relationship could be better determined in future studies.[24]

This study has some limitations. First, although the overall number of hemorrhages was comparable to previously published data, the number of symptomatic hemorrhages (defined as PH-2) in this series is low compared to some other studies.[22, 25] Most symptomatic hemorrhages (n=23) are not included because the inclusion criteria for this study required a CTP at follow-up. Patients with symptomatic HT may have been too agitated or hemodynamically unstable to lie still long enough to perform this follow-up CTP and many of the PH-2 outcomes from the DUST database could not be included in this analysis because follow-up CTP was missing. Another explanation for the low number of PH-2's may be the relatively short time to treatment in our study. It is known that longer time to treatment is related to occurrence of HT.[25] We included smaller hemorrhages (HI-1 and HI-2) in our analysis since they are also related to poor outcome in larger studies.[26-28] Nevertheless, due to the low number of PH-2, our results must be interpreted with caution and are mainly applicable for populations with smaller hemorrhages.

Second, the timing of most follow-up scans was around 3 days. Reperfusion and recanalization are known to continue up to several weeks but the 'time is brain' concept states that reperfusion is only relevant if it occurs within several hours after onset of ischemia.[29] It could be argued that reperfusion measurement at an earlier time point would be more appropriate. But for practical purposes and to minimize discomfort for participating patients we had to compromise between timing of HT detection and early reperfusion assessment. Moreover, because patients did receive an additional NCCT in case of clinical deterioration after the scheduled follow-up scans were made, it is unlikely significant hemorrhages were missed.

Third, we excluded patients with intra-arterial treatment as most of these patients were treated with a combination of mechanical thrombectomy and intra-arterial thrombolysis, which probably has an added but unknown effect on the integrity of the BBB.

Fourth, reperfusion status was not quantitatively assessed but dichotomized as reperfusion or no-reperfusion by visual comparison of the admission and follow-up CTP images. Little is known about the quantitative assessment of reperfusion with CTP and no universal thresholds for the assessment of change of CTP deficits are available. Moreover, the discrepancy rate for quantitative assessment of reperfusion with the Thrombolysis in Myocardial Infarction (TIMI) reperfusion score on angiography has been described to be as high as 41%, which seems to justify using a simple qualitative assessment.[30] Qualitative interpretation of CTP has shown good to excellent agreement rates between observers.[31-33]



# Conclusions

The occurrence of hemorrhagic transformation does not seem to be associated with reperfusion. This suggests that other causes, like ischemic injury or the effects of IV-rtPA, are more important in the occurrence of hemorrhagic transformation in acute ischemic stroke.

# References


1. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol. 2006;60:508-517

2. Soares BP, Tong E, Hom J, Cheng SC, Bredno J, Boussel L, Smith WS, Wintermark M. Reperfusion is a more accurate predictor of follow-up infarct volume than recanalization: a proof of concept using CT in acute ischemic stroke patients. Stroke. 2010;41:e34-40

3. Fiehler J, Remmele C, Kucinski T, Rosenkranz M, Thomalla G, Weiller C, Zeumer H, Rother J. Reperfusion after severe local perfusion deficit precedes hemorrhagic transformation: an MRI study in acute stroke patients. Cerebrovasc Dis. 2005;19:117-124

4. Warach S. Evidence of Reperfusion Injury, Exacerbated by Thrombolytic Therapy, in Human Focal Brain Ischemia Using a Novel Imaging Marker of Early Blood-Brain Barrier Disruption. Stroke. 2004;35:2659-2661

5. Molina CA, Alvarez-Sabin J. Recanalization and reperfusion therapies for acute ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl 1:162-167

6. Rudolf J, Grond M, Stenzel C, Neveling M, Heiss WD. Incidence of space-occupying brain edema following systemic thrombolysis of acute supratentorial ischemia. Cerebrovasc Dis. 1998;8:166-171

7. 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;32:1330-1335

8. Molina CA, Alvarez-Sabin J, Montaner J, Abilleira S, Arenillas JF, Coscojuela P, Romero F, Codina A. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. Stroke. 2002;33:1551-1556

9. Khatri P, Wechsler LR, Broderick JP. Intracranial hemorrhage associated with revascularization therapies. Stroke. 2007;38:431-440

10. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375:1695-1703

11. Kassner A, Roberts TPL, Moran B, Silver FL, Mikulis DJ. Recombinant Tissue Plasminogen Activator Increases Blood-Brain Barrier Disruption in Acute Ischemic Stroke: An MR Imaging Permeability Study. AJNR Am J Neuroradiol. 2009;30:1864-1869

12. NINDS rssg. 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;333:1581-1587

13. Saqqur M, Tsivgoulis G, Molina CA, Demchuk AM, Siddiqui M, Alvarez-Sabin J, Uchino K, Calleja S, Alexandrov AV. Symptomatic intracerebral hemorrhage and recanalization after IV rt-PA: a multicenter study. Neurology. 2008;71:1304-1312

14. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37

15. 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. Lancet. 2000;355:1670-1674

16. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. Magn Reson Med. 1996;36:715-725

17. Axel L. A method of calculating brain blood flow with a CT dynamic scanner. Adv Neurol. 1981;30:67-71

18. Wintermark M, Maeder P, Thiran JP, Schnyder P, Meuli R. Quantitative assessment of regional cerebral blood flows by perfusion CT studies at low injection rates: a critical review of the underlying theoretical models. Eur Radiol. 2001;11:1220-1230

19. Niesten JM, van der Schaaf IC, Riordan AJ, de Jong HW, Mali WP, Velthuis BK. Optimisation of vascular input and output functions in CT-perfusion imaging using 256(or more)-slice multidetector CT. Eur Radiol. 2013;23:1242-1249

20. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025

21. Latour LL, Kang DW, Ezzeddine MA, Chalela JA, Warach S. Early blood-brain barrier disruption in human focal brain ischemia. Ann Neurol. 2004;56:468-477

22. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275-282

23. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet. 1998;352:1245-1251

24. Mendrik AM, Vonken EJ, van Ginneken B, de Jong HW, Riordan A, van Seeters T, Smit EJ,

Viergever MA, Prokop M. TIPS bilateral noise reduction in 4D CT perfusion scans produces high-quality cerebral blood flow maps. Phys Med Biol. 2011;56:3857-3872

25. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC, Jr., Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363:768-774

26. Dzialowski I, Pexman JH, Barber PA, Demchuk AM, Buchan AM, Hill MD. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke effectiveness study registry. Stroke. 2007;38:75-79

27. Park JH, Ko Y, Kim WJ, Jang MS, Yang MH, Han MK, Oh CW, Park SH, Lee J, Bae HJ, Gorelick PB. Is asymptomatic hemorrhagic transformation really innocuous? Neurology. 2012;78:421-426

28. Kimura K, Iguchi Y, Shibazaki K, Aoki J, Terasawa Y. Hemorrhagic transformation of ischemic brain tissue after t-PA thrombolysis as detected by MRI may be asymptomatic, but impair neurological recovery. J Neurol Sci. 2008;272:136-142

29. Saver JL. Time is brain--quantified. Stroke. 2006;37:263-266

30. Tomsick T. TIMI, TIBI, TICI: I came, I saw, I got confused. AJNR Am J Neuroradiol. 2007;28:382-384

31. Sanelli PC, Nicola G, Johnson R, Tsiouris AJ, Ougorets I, Knight C, Frommer B, Veronelli S, Zimmerman RD. Effect of training and experience on qualitative and quantitative CT perfusion data. AJNR Am J Neuroradiol 2007;28:428-432

32. Biesbroek JM, Niesten JM, Dankbaar JW, Biessels GJ, Velthuis BK, Reitsma JB, van der Schaaf IC. Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2013;35:493-501

33. van Seeters T, Biessels GJ, Niesten JM, van der Schaaf IC, Dankbaar JW, Horsch AD, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Reliability of Visual Assessment of Non-Contrast CT, CT Angiography Source Images and CT Perfusion in Patients with Suspected Ischemic Stroke. PLoS One. 2013;8:e75615

# CHAPTER 5

# CT perfusion analysis by nonlinear regression for predicting hemorrhagic transformation in ischemic stroke

Edwin Bennink, Alexander D. Horsch, Jan Willem Dankbaar, Birgitta K. Velthuis, Max A. Viergever, Hugo W. A. M. de Jong

Adapted from:
**Medical Physics 42, 4610 (2015)**

# Abstract

## Background

Intra-venous thrombolysis can improve clinical outcome in acute ischemic stroke patients, but increases the risk of hemorrhagic transformation (HT). Blood-brain barrier damage, which can be quantified by the vascular permeability for contrast agents, is a potential predictor for HT. This study aimed to assess whether this prediction can be improved by measuring vascular permeability using a novel fast nonlinear regression (NLR) method instead of Patlak analysis.

## Methods

From a prospective ischemic stroke multicenter cohort study, 20 patients with HT on follow-up imaging and 40 patients without HT were selected. The permeability transfer constant $K^{trans}$ was measured in three ways; using standard Patlak analysis, Patlak analysis with a fixed offset, and the NLR method. In addition, the permeability-surface area product (PS) and the conventional perfusion parameters (blood volume, flow, and mean transit time) were measured using the NLR method. Relative values were calculated in two ways, i.e. by dividing the average in the infarct core by the average in the contra-lateral hemisphere, and by dividing the average in the ipsi-lateral hemisphere by the average in the contra-lateral hemisphere. Mann-Whitney U tests and receiver operating characteristic (ROC) analyses were performed to assess the discriminative power of each of the relative parameters.

## Results

Both the infarct core and whole hemisphere averaged relative $K^{trans}$ ($rK^{trans}$) values, measured with the NLR method, were significantly higher in the patients who developed HT as compared with those who did not. The $rK^{trans}$ measured with standard Patlak analysis was not significantly different. The relative PS (rPS), measured with NLR, had the highest discriminative power (P=0.002). ROC analysis of rPS showed an area under the curve (AUC) of 0.75 (95% confidence interval: 0.62 to 0.89) and a sensitivity of 0.75 at a specificity of 0.75. The AUCs of the Patlak $rK^{trans}$, the Patlak $rK^{trans}$ with fixed offset and the NLR $rK^{trans}$ were 0.58, 0.66, and 0.67 respectively.

## Conclusion

CT perfusion analysis may aid in predicting HT, but standard Patlak analysis did not provide estimates for $rK^{trans}$ that were significantly higher in the HT group. rPS, measured in the infarct core with NLR, had superior discriminative power compared with $K^{trans}$ measured with either Patlak analysis with a fixed offset or NLR, and conventional perfusion parameters.

# Introduction

Intra-venous thrombolysis (IVT) can improve clinical outcome in acute ischemic stroke patients but may increase the risk of developing hemorrhagic transformation (HT) by 50%.[1, 2, 3, 4] CT perfusion (CTP) imaging, or dynamic contrast enhanced CT (DCE-CT), is frequently used for diagnosing acute ischemic stroke. Besides measuring blood volume, flow, and transit time, this technique also allows for the estimation of vascular permeability for contrast agent by extending the duration of acquisition. Blood-brain barrier damage, which can be quantified by measuring vascular permeability, may be a predictor for HT in stroke.[5–7] CTP could therefore potentially provide the means to predict the risk of developing HT with IVT treatment.

In CT stroke imaging, permeability is most frequently estimated by applying linearized regression to local time-attenuation curves (TACs), i.e. by graphical analysis of a Patlak plot.[6–10] This method is straightforward and fast, but linearized regression has some inherent weaknesses compared to nonlinear regression (NLR). Most important, only the steady-state time-frames (after the first-pass bolus) can be taken into account. In contrast, NLR allows for the analysis of entire TACs, providing an integral method for measuring permeability along with the cerebral blood volume (CBV), flow (CBF), and mean transit time (MTT). A previous study by our group found that the 95% confidence interval (CI) for the permeability transfer constant $K^{trans}$ as estimated with standard Patlak analysis was three times larger compared to NLR analysis.[11] The same study found that fixing the blood volume in Patlak analysis to a value estimated with a gamma variate fit showed an improved 95% CI, but still inferior to NLR.

Because NLR allows estimating the permeability transfer constant $K^{trans}$ with a theoretically higher reliability, it is hypothesized that this method will also give estimates with a higher discriminative power than Patlak analysis. The purpose of this study was to determine if the predictive value of permeability and perfusion parameters for HT development, measured using extended CTP imaging, can be improved by using the NLR method instead of Patlak analysis.

# Materials and methods

## Study Design

Patients were included from the Dutch acute stroke study (DUST), of which the study protocol has been described previously.[12] In brief, DUST is a large prospective multicenter cohort study, which aims to assess the prognostic value of CTP and CT angiography (CTA) in ischemic stroke patients for 90-day clinical outcome (NCT0080113). Patients were enrolled

in 14 Dutch hospitals between May 2009 and end of August 2013.

Inclusion criteria for this study were: age above 18 years, suspected ischemic stroke of less than 9 hours duration and a National Institutes of Health Stroke Scale (NIHSS) score ≥2, or 1 if an indication for recombinant tissue Plasminogen Activator (rtPA) therapy is present.[13] Exclusion criteria were known renal failure or contrast allergy. This study was approved by the local institutional ethical review boards of the participating centers, and all patients or family gave signed informed consent.

From this study database a consecutive series of patients was selected matching the following additional inclusion criteria: 0.625-1.25 mm thin slice reconstructed, extended (meaning 210 second duration) CTP acquisition on admission, and follow-up non-contrast CT (NCCT) imaging at three days or in case of clinical deterioration. We selected the first 20 consecutive cases with HT on follow-up NCCT and 40 controls without HT on follow-up NCCT. HT was defined as the presence of any European Cooperative Acute Stroke Study (ECASS) HT subtype.[14] All patients in the control group received IVT within a 4.5 hour window from time to onset. Because infarct location was not a selection criterion, these locations were randomly distributed to their natural prevalence.



## Imaging protocol

CTP was performed on admission before possible thrombolytic treatment. Multi-detector (40-256 slice) CT scanners were used at 80 kVp and 125 to 150 mAs/rotation. All scans had a total acquisition time of at least 210 seconds, divided into 25 frames with an approximately 2 second interval, a 15 second pause, and 6 frames with an approximately 30 second interval, as shown in Figure 1B. The total effective radiation dose of this protocol was 2.7 to 3.3 mSv (0.09 to 0.1 mSv per frame). Before scanning, 40 mL of non-ionic contrast agent was injected intra-venously at a rate of 6 mL/s, followed by a 40 mL saline flush. The average arterial bolus arrival time (BAT), i.e. the time between the start of the scan and the first appearance of contrast enhancement in the cerebral arteries, was 6.9 s.

The scans had a coverage of 40-65 mm from at least the level of the basal ganglia to the lateral ventricles to be able to assess Alberta Stroke Program Early CT score (ASPECTS) levels 1 and 2.[15] The slices, with a field of view of approximately 200×200 $mm^2$, were reconstructed in a 512×512 matrix using filtered backprojection with a medium smooth reconstruction kernel (vendor-specific).

## Preprocessing

Because moderate and severe head movement is common in CTP imaging of acute ischemic stroke patients, the time series of 0.625 to 1.25 mm thick slices were registered in 3D using a rigid registration algorithm (Elastix).[16, 17] After registration adjacent axial slices were averaged to obtain 8 to 13 contiguous slabs of 5 mm per volume, which is common practice for clinical

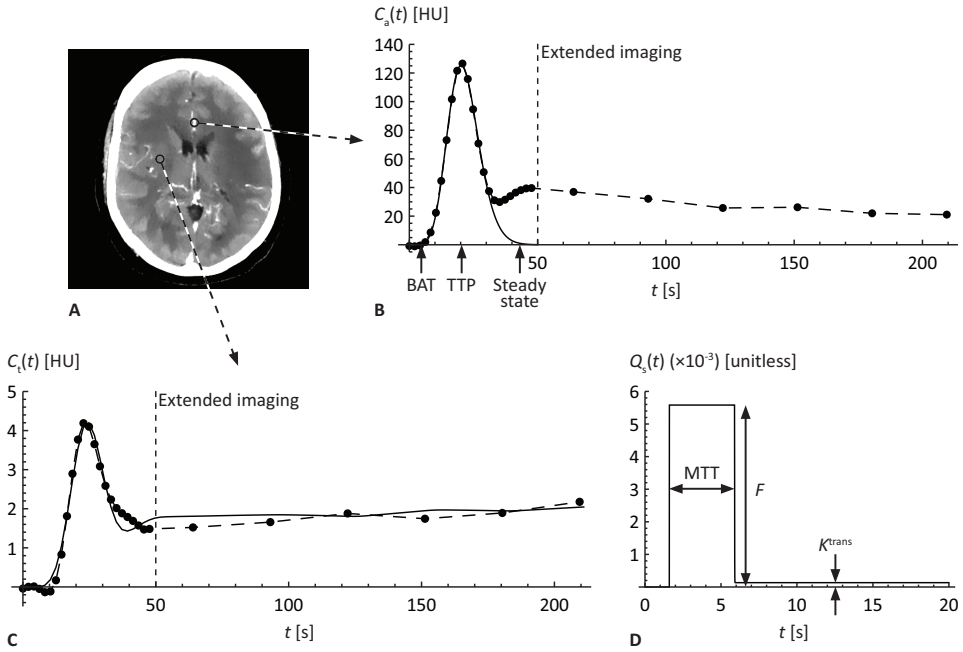



Figure 1:

A) A filtered CT perfusion slice (time frame at the time to peak of the arterial input function).
B) A typical arterial input function $C_a(t)$ measured with extended CT perfusion imaging (real, filtered data), showing the bolus arrival time (BAT), time to peak (TTP), and the start of the steady state as estimated using a gamma variate fit (solid line).
C) A time-attenuation curve $C_t(t)$ measured in a single voxel (real, filtered data) and the corresponding theoretical curve fitted using nonlinear regression (solid line).
D) The impulse response function (IRF) $Q_s(t)$ (Equation 6) behind the theoretical curve that fits the time-attenuation curve in figure C the best. This IRF has a delay of 1.6 seconds, a CBV of 2.4 mL/100g, a CBF of 34 mL/min/100g, an MTT of 4.3 seconds, and a permeability transfer rate ($K^{trans}$) of 0.81 mL/min/100g.

evaluation, mainly to limit the noise and processing time. The registered time frames were visually inspected for artifacts; these are mostly streak artifacts caused by motion during frame acquisition. Poor frames were removed from the data. Next, a temporal Gaussian filter with a SD of 4 seconds, followed by a 3D bilateral filter (TIPS) with a spatial SD ($\sigma_d$) of 4 mm and a profile similarity SD ($\sigma_\zeta$) of 50 HU$^2$ were applied to further reduce the noise.[18] These settings

correspond to what was used in a previous study of group, and result in perfusion maps with a visually well balanced resolution and noise level.[11] A gamma variate curve was fitted to the arterial input function (AIF) to estimate its area under the curve (AUC), time to peak (TTP), the arterial bolus arrival time, and the onset of the steady state (Figure 1B).

### Estimating Permeability and Perfusion Parameters

The capillary blood-brain barrier (BBB) consists of a compact layer of endothelial cells with tight junctions, which restricts the passage of large hydrophilic molecules like CT contrast material. For this reason the CTP-measured permeability transfer constant $K^{trans}$, a metric of BBB integrity, is nearly zero in the healthy brain. Ischemia due to stroke may, however, alter BBB integrity, allowing the diffusion of blood and contrast molecules into the extra-vascular space.

Unknown at the time of measurement, the leakage may either be in the permeability-limited domain or in the flow-limited domain. In the first case the outflow to the extra-vascular space as measured by $K^{trans}$ will not increase when the flow increases, whereas in the latter case it will increase linearly with the flow. In either case, a patient with BBB damage is likely to show increased $K^{trans}$ values. $K^{trans}$ was measured in three ways. First, using standard linear Patlak analysis, second, using Patlak analysis with an offset that is fixed to a blood volume that was estimated by an independent method, and third, using an NLR method.[9, 10, 11, 21] Only the NLR method is capable of estimating the flow, *F*, and therefore of calculating the PS using the Renkin-Crone equation[19, 20]:

Equation 1

$$K^{\text{trans}} = F\left(1 - e^{-PS/F}\right)$$

## Patlak Analysis

An underlying assumption of Patlak analysis is that the potential vascular leakage of contrast agent through the BBB can be regarded as unidirectional during the acquisition time of the CTP scan, which is a valid assumption in case of low permeability and relatively short measurement duration, as in CT brain perfusion. Following this, the total tracer concentration in a tissue voxel at time point *t*, $C_t(t)$, can be described as a function of the capillary concentration $C_c(t)$, the intra-vascular blood volume $V_t$, and the transfer constant $K^{trans}$ that represents the flow from the intra- to the extra-vascular space:

Equation 2

$$C_t(t) = K^{\text{trans}} \int_0^t C_c(\tau)\mathrm{d}\tau + V_i C_c(t)$$

In a Patlak plot, this relationship is transformed in such a way that the data points fall on a straight line when the capillary concentration reaches a steady state (Figure 2.)

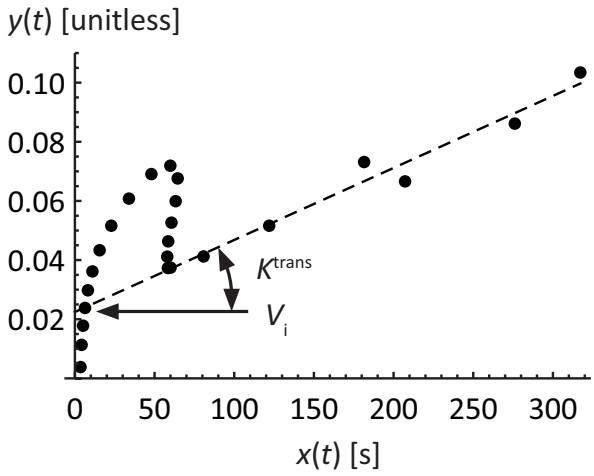



Figure 2: Graphical Patlak analysis using a parametric Patlak plot. *x(t)* and *y(t)* are defined in Equation 3 and Equation 4. A linear fit (dashed) to the steady-state data points gives estimates for the permeability ($K^{trans}$; slope) and blood volume ($V_i$; intercept). The Patlak plot shown was generated from the AIF and TAC in Figure 1B and C. Note that, due a small delay between bolus arrival in the AIF and the TAC, the first-pass part of the curve is slightly skewed.[6] This phenomenon has no significant effect on the data points in the steady state.

Equation 3

$$y(t) = \frac{C_t(t)}{C_c(t)} = K^{\text{trans}} x(t) + V_i$$

Equation 4

$$x(t) = \frac{\int_0^t C_c(\tau)\mathrm{d}\tau}{C_c(t)}$$

This steady state is, corresponding to our previous study, defined as the arterial TTP plus 3.5× the standard deviation of the first-pass bolus, measured using a gamma variate curve fit.[11]

Equation 3 shows that when a linear fit $y(t) = K^{trans}\, x(t) + V_i$ is applied to these steady state data points in the plot, the slope of the fit and its intersection with the y-axis give an estimation of respectively the transfer constant $K^{trans}$, and the blood volume $V_i$. Note that, due to a small delay between bolus arrival in the AIF and the TAC, the first-pass part of the curve is slightly skewed.[6] This phenomenon has no significant effect on the data points in the steady state.

The value for $V_i$ can either be estimated from the linear fit, or it can be fixed to predefined value. In this study $V_i$ is both estimated from the fit as well as fixed to a value that was found by calculating the ratio between the integrals of gamma variate functions fitted to the AIF and to the tissue TAC.

# NonLinear Regression

The nonlinear regression (NLR) method uses a mathematical model to describe the impulse response function (IRF) of the perfused tissue. An IRF can be thought of the time-attenuation curve of a small tissue volume in response to an infinitesimal short AIF. The convolution of the measured AIF, $C_a(t)$, with a computed IRF, IRF($t$), gives an estimate of the true TAC of the tissue volume, $C_t(t)$:

Equation 5

$$C_t(t) = C_a(t) \otimes IRF(t) + \varepsilon(t)$$

NLR is used to iteratively adapt the free parameters in the mathematical model to minimize the mean of the square of the error ε(t) between this estimate and the measured TAC.

Whereas a linearization such as the Patlak method allows just two degrees of freedom (i.e. blood volume and $K^{trans}$), NLR allows more complex models with more degrees of freedom. In order to model brain tissue perfusion with permeability, at least three parameters are required. These are MTT and CBF, describing bulk capillary perfusion, and $K^{trans}$, describing the BBB permeability. Furthermore, it was found that it is beneficial to incorporate a fourth parameter, a correction for the arterial delay, i.e. the time required for the bolus to travel from the AIF location to the tissue of interest.[22]

Since the use of IRFs allows a more comprehensive estimation of the perfusion process, including delay and transit time, the information in the entire attenuation curve is used for

calculating the estimates. This is a major advantage over linearized regression such as Patlak analysis, which only uses the data points in the steady state, disregarding potential useful information in the preceding part.

Because the diagnosis of acute ischemic stroke is time-critical for timely therapy, a simplified IRF $Q_s(t)$ was used that allowed for fast NLR fitting.[11] By assuming both irreversible leakage and an equal transit time for all capillaries within a voxel, the shape of the IRF can be reduced to a combination of two step functions (Figure 1D), allowing a very computational efficient calculation of Equation 5:

Equation 6

$$Q_S(t) = F\,\mathrm{U}(t - t_\Delta) - (F - K^{\mathrm{trans}})\mathrm{U}(t - t_\Delta - MTT)$$

In Equation 6, $U(t)$ is the unit step function, F is the plasma flow, MTT is the mean transit time, and $t_\Delta$ is the delay in bolus arrival between the AIF and the tissue curve. Note that the convolution in Equation 5, with IRF(t) = $Q_s(t)$ as given in Equation 6, can also be defined in terms of differential equations, i.e. as the solution of:

Equation 7

$$\frac{\mathrm{d}\,C_t(t)}{\mathrm{d}\,t} = FC_a(t - t_\Delta) - (F - K^{\mathrm{trans}})C_a(t - t_\Delta - MTT)$$

In addition to $K^{trans}$, CBV, CBF, and MTT, PS can be estimated following the Renkin-Crone equation (Equation 1). Note that this parameter is interrelated with other parameters, as is the intra-vascular blood volume $V_i$ = MTT · F.

NLR was applied using a generic Nelder-Mead simplex method.[23, 24] The initial values for minimization were $V_i$=4 mL/100g, MTT=4 s, $K^{trans}$=1.5 mL/min/100g, and $t_\Delta$=1 s, and the initial step sizes were respectively 2 mL/100g, 5 s, 1.5 mL/min/100g, and 2 s.

A crucial step in numerical NLR (and signal-processing in general) is proper band-limiting. If $Q_s(t)$ is not band-limited, then high-frequency aliasing causes spurious local minima that spoil the regression. To suppress frequency components above the Nyquist frequency, both $Q_s(t)$ and $C_t(t)$ were band-limited using a Bartlett kernel (triangular). To fulfill the Nyquist criterion, the FWHM of the kernel was set to 2× the sample interval, which is in this case 2×2 seconds.

A previous study by our group showed that NLR analysis as described above, using the IRF in Equation 6, resulted in unbiased estimates of $K^{trans}$ under low-noise conditions.[11] Under realistic noise conditions, both the NLR and Patlak methods showed a small positive bias for small $K^{trans}$ values. It was furthermore found that the $K^{trans}$ values measured by the simplified method were not affected by MTT, and that more complex models did not provide more reliable estimations of $K^{trans}$ in stroke patients. NLR confidence intervals were three times smaller than standard Patlak analysis and more than 1.5 times smaller than Patlak analysis with fixed offset.

**Table 1. Baseline clinical and imaging characteristics.**

| | All patients N=60 | Control group N= 40 (67 %) | HT group N=20 (33 %) | P-value |
|---|---|---|---|---|
| **Clinical parameters** | | | | |
| Age, mean (SD) | 69 (13) | 67 (13) | 73 (12) | 0.07 |
| Female sex, n (%) | 24 (40) | 18 (45) | 6 (30) | 0.27 |
| Prior stroke, n (%) | 10 (17) | 6 (15) | 4 (20) | 0.63 |
| Baseline NIHSS, mean (SD) | 11 (6) | 11 (5) | 12 (7) | 0.40 |
| Time to arrival, minutes, median (IQ) | 65 (47-121) | 73 (37-120) | 62 (50-133) | 0.94 |
| **CT perfusion imaging** | | | | |
| Size infarct core, $mm^2$, median (IQ) * | 458 (75-1695) | 290 (58-1204) | 1161 (179-3002) | 0.12 |
| Size penumbra area, $mm^2$, median (IQ) * | 1938 (627-3819) | 1938 (713-2895) | 2835 (316-5119) | 0.38 |
| Time to imaging, minutes, median (IQ) | 98 (69-145) | 98 (66-145) | 96 (72-153) | 0.65 |
| **Treatment** | | | | |
| IVT, n (%) | 55 (92) | 40 (100) | 15 (75) | 0.001 |
| IAT or MT, n (%) | 4 (7) | 3 (8) | 1 (5) | 0.73 |
| Time to treatment, minutes, median (IQ) † | 113 (80-165) | 115 (78-165) | 110 (87-167) | 0.94 |

* Total area of the infarct core and penumbra cross-sections at both ASPECTS levels.[28]
† For 54 patients (5 did not receive IVT, and missing value in 1 HT patient).
HT, hemorrhagic transformation; IAT, intra-arterial thrombolysis; IVT, intra-venous thrombolysis; MT, mechanical thrombectomy.

## Postprocessing

The contrast-free time frames (before the bolus arrival time) were averaged to obtain a NCCT image. Only the voxels that had a CT value >17 Hounsfield units (HU) or <55 HU on this NCCT were classified as brain tissue and included in the analysis. Voxels with a blood volume >9 mL/100g were classified as vessels and excluded from the analysis. A correction factor $k_H=(1-H_{LV})/(1-H_{SV})$ was applied to correct the tracer concentration for the difference between the hematocrit in large vessels (AIF), $H_{LV}$, and small vessels (tissue; arterioles and capillaries), $H_{SV}$.[25] The values used for $H_{LV}$ and $H_{SV}$ were respectively 0.45 and 0.2526.

## Statistical Analysis

All parameters were estimated in each of the voxels that were classified as brain tissue on the NCCT. Infarct cores were defined as all brain tissue voxels on the ipsi-lateral side having a CBV less than 2 mL/100g, as suggested by Wintermark et al.[27] The measured parameters were averaged in the infarct core as well as in the brain tissue in both entire hemispheres. Next, relative values averages were obtained in two ways. First, by dividing the average in the infarct core by the average in the entire contra-lateral hemisphere. Second, by dividing the average in the entire ipsi-lateral hemisphere by the average in the entire contra-lateral hemisphere. A symmetry plane was manually aligned to the midsagittal plane in order to separate the hemispheres.

Pearson correlation coefficients and linear fits were calculated to quantify the relation between the three different measurements for $K^{trans}$. Wilcoxon signed rank tests were applied to check if the relative parameters ($rK^{trans}$, rPS, rCBV, rCBF, and rMTT) were significantly different between the hemispheres. To identify the parameters that were significantly different between the HT group and control group, a Mann-Whitney U test was applied. Results were considered significant for $P<0.05$. Receiver operating characteristic (ROC) curves were used to assess the discriminating power of those parameters that were found to be significantly different.

# Results

Demographic and clinical data of the selected patients are summarized in Table 1. There were no significant differences in age, sex, prior stroke, baseline NIHSS score, time to arrival, or time to imaging between the HT and control group. The medians of the infarct core and penumbra sizes (total area of the cross sections at both ASPECTS levels) were higher in the HT group, but not significantly different.[28]

Visual inspection revealed that some of the patients (20%) showed ring-shaped scanner artifacts in their permeability maps ($K^{trans}$ and PS), with the worst case shown in the bottom

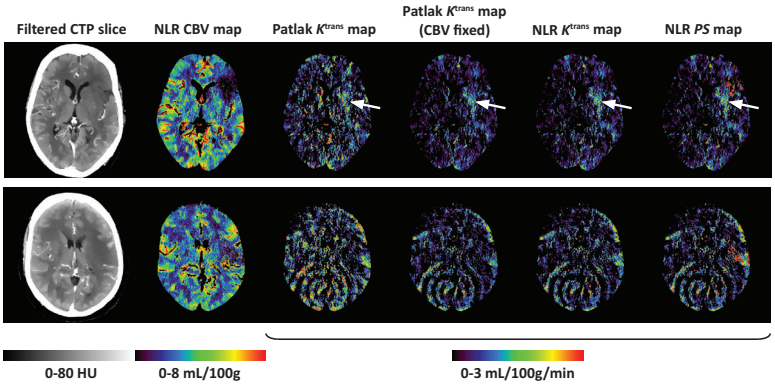



Figure 3: A filtered CT perfusion slice (time frame at the time to peak of the arterial input function), the NLR blood volume (CBV) map, the three $K^{trans}$ maps, and the NLR permeability-surface area (PS) map of two patients in the HT group. The CBV maps both show a clearly visible infarct core in the middle cerebral artery territory in the left hemisphere. The standard Patlak maps (third column) appear noisier than the CBV fixed and NLR $K^{trans}$ maps. The $K^{trans}$ and PS maps in the top row show elevated permeability in the entire ipsi-lateral hemisphere and a permeability 'hot spot' medial to the infarct core (indicated by the arrows). The maps in the bottom row are affected by ring-shaped scanner artifacts (worst case shown).



**Table 2: The median (IQ range) and P-value of each relative perfusion parameter in the infarct cores and in the whole ipsi-lateral hemispheres.**

| | Infarct core vs whole contralateral hemisphere | | | Whole ipsilateral hemisphere vs whole contralateral hemisphere | | |
|---|---|---|---|---|---|---|
| **Parameter** | **HT (N=20)** | **Control (N=40** | **P-value** | **HT (N=20)** | **Control (N=40)** | **P-value** |
| Patlak $rK^{trans}$ | 0.95 (0.19) | 0.93 (0.12) | 0.30 | 1.03 (0.25) | 1.04 (0.14) | 0.83 |
| Patlak $rK^{trans}$ (fixed offset) | 0.91 (0.30) | 0.78 (0.13) | 0.04* | 1.22 (0.33) | 1.03 (0.12) | 0.11 |
| NLR $rK^{trans}$ | 1.02 (0.42) | 0.76 (0.17) | 0.03* | 1.28 (0.46) | 1.07 (0.18) | 0.04* |
| NLR rPS | 1.70 (1.06) | 0.89 (0.35) | 0.002* | 1.66 (0.86) | 1.11 (0.77) | 0.005* |
| NLR rCBV | 0.45 (0.20) | 0.55 (0.11) | 0.10 | 0.99 (0.13) | 1.00 (0.07) | 0.26 |
| NLR rCBF | 0.47 (0.23) | 0.58 (0.21) | 0.04* | 0.78 (0.25) | 0.90 (0.14) | 0.05* |
| NLR rMTT | 1.51 (0.69) | 1.09 (0.42) | 0.09 | 1.72 (0.90) | 1.25 (0.37) | 0.03* |

* Significant, i.e. P<0.05.

row in Figure 3. These distortions were just slightly visible on the filtered CTP data and on the other perfusion maps (CBV, CBF, and MTT) generated by the NLR method.

The hemisphere-averages of all estimated parameters, except for the CBV, were found to be significantly different between the ipsi- and contra-lateral sides ($P<0.05$) in both the HT group and the control group.

All three methods addressed in this study, i.e. Patlak, Patlak with fixed offset, and NLR, provide estimates for the permeability transfer constant $K^{trans}$. However, only the Patlak method with fixed offset and the NLR method gave estimates for relative $K^{trans}$ ($rK^{trans}$) that were significantly higher in the patients who developed HT ($P=0.04$ and $P=0.03$ for the infarct cores, Table 2 and Figure 4). The values for Patlak $K^{trans}$ with fixed offset showed a strong correlation with the NLR $K^{trans}$ values, which is emphasized by the $K^{trans}$ maps in Figure 3. The Pearson coefficient between the average $K^{trans}$ values measured in the infarct core between these methods was 0.99, and the slope of a linear fit through the origin was 1.02. The standard Patlak $K^{trans}$ showed a weaker correlation with NLR $K^{trans}$, with a Pearson coefficient of 0.83 and a slope of 2.05.

The relative permeability-surface area product (rPS) had the highest discriminative power. This parameter had both the lowest P-value in the Mann-Whitney U test ($P=0.002$ for the



**Table 3: Receiver operating characteristic (ROC) curves of all parameters.**

| | Infarct core vs whole contralateral hemisphere | | | Whole ipsilateral hemisphere vs whole contralateral hemisphere | | |
|---|---|---|---|---|---|---|
| **Parameter** | **AUC** | **95% CI** | **P-value** | **AUC** | **95% CI** | **P-value** |
| Patlak $rK^{trans}$ | 0.58 | 0.43 – 0.74 | 0.29 | 0.52 | 0.35 – 0.69 | 0.83 |
| Patlak $rK^{trans}$ (fixed offset) | 0.66 | 0.51 – 0.81 | 0.04* | 0.63 | 0.46 – 0.80 | 0.11 |
| NLR $rK^{trans}$ | 0.67 | 0.52 – 0.82 | 0.03* | 0.67 | 0.51 – 0.82 | 0.04* |
| NLR rPS | 0.75 | 0.62 – 0.89 | 0.001* | 0.73 | 0.58 – 0.88 | 0.005* |
| NLR CBV | 0.63 | 0.47 – 0.80 | 0.10 | 0.59 | 0.43 – 0.75 | 0.26 |
| NLR rCBF | 0.67 | 0.52 – 0.81 | 0.04* | 0.66 | 0.50 – 0.82 | 0.05* |
| NLR rMTT | 0.64 | 0.48 – 0.80 | 0.09 | 0.68 | 0.52 – 0.83 | 0.03* |

* Significant, i.e. $P<0.05$.
The curves for the parameters with significant discriminating value are shown in Figure 5.

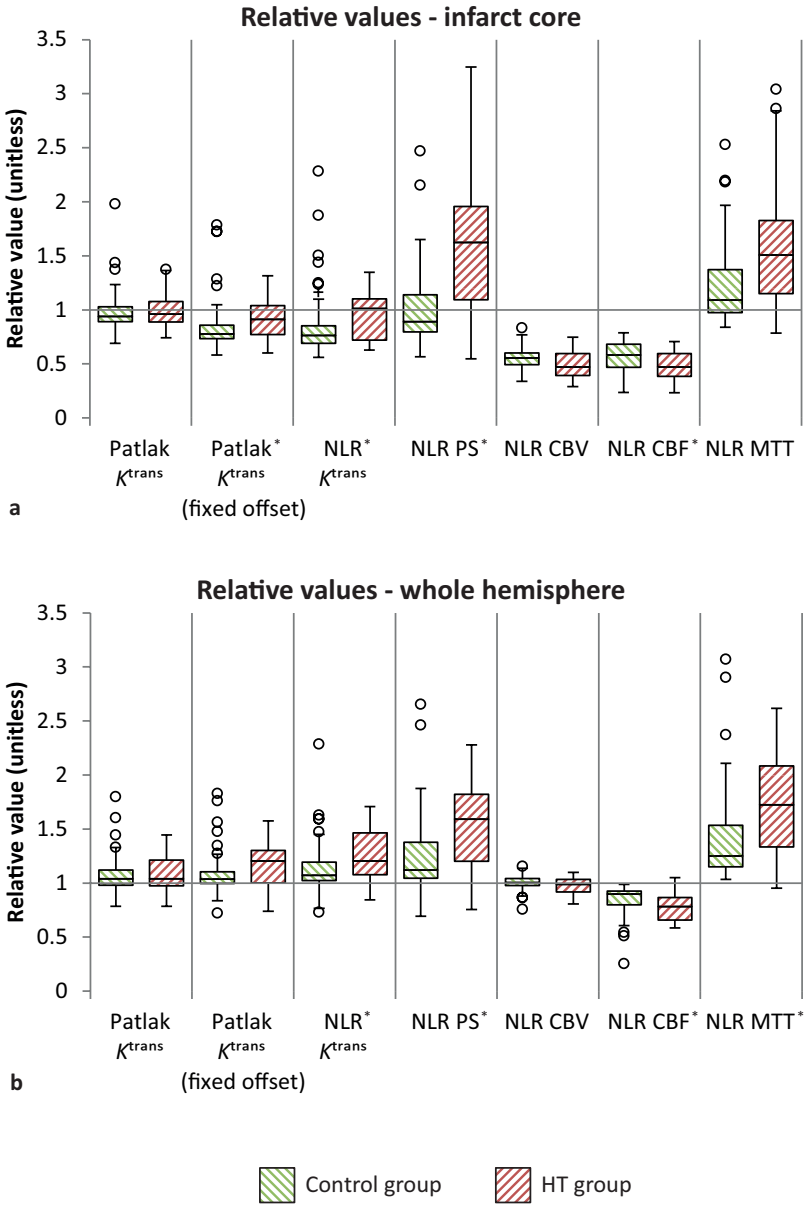



Figure 4: The distributions of the average relative permeability- and perfusion-parameters in the infarct cores (a) and in the whole ipsi-lateral hemispheres (b). The left boxes represent the control group and the right boxes the HT group. The parameters marked (*) are significantly different between both groups (P<0.05).

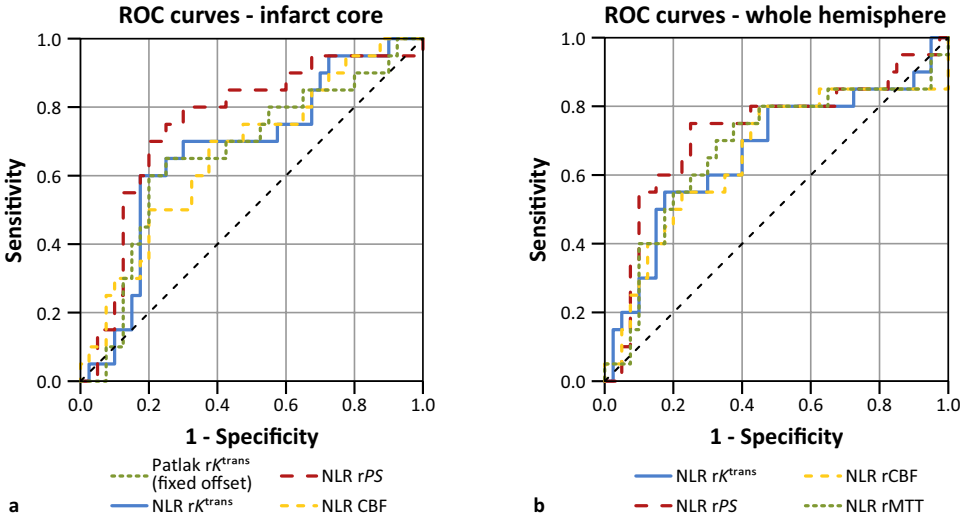





Figure 5: Receiver operating characteristic (ROC) curves of the parameters that were found to be significantly different between the HT group and the control group (Table 2). The areas under the curves are given in Table 3.

infarct cores) and the highest area under its ROC curve (0.75, 95% CI: 0.62 to 0.89, Table 3 and Figure 5). The rPS had a sensitivity of 0.75 at a specificity of 0.75 (threshold at rPS=1.12), and a sensitivity of 0.50 at a specificity of 0.88 (threshold at rPS=1.70).

The parameters, except for rMTT, had slightly better discriminative power when measured in the infarct core than when measured in the whole ipsi-lateral hemisphere.

In addition, the relative CBF (rCBF) was significantly lower in the HT group (P=0.04 for the infarct cores). The relative MTT (rMTT) was significantly higher in the HT group, but only when measured in the entire hemisphere (P=0.03). No significant differences in relative CBV (rCBV) between the groups were observed.

For none of the measured parameters significant differences were found between the subgroup of patients that developed HT and received IVT and the subgroup that developed HT but did not receive IVT. The $rK^{trans}$ and rPS parameters were on average lower in the subgroup that did not receive IVT treatment.

# Discussion

Nonlinear regression allows for simultaneous measurement of permeability along with CBV, CBF, and MTT. Whereas the frequently used Patlak method only takes the steady-state time frames (after the first-pass bolus) into account, NLR allows for the analysis of the entire TACs. We have shown before that this feature resulted in smaller 95% CIs for the permeability estimates.[11] This study emphasizes the use of NLR over Patlak analysis, because it also provides better predictors for developing HT.

The parameter $rK^{trans}$ estimated with fixed-offset Patlak analysis showed improved discriminating power compared with standard Patlak analysis. This corresponds to the previous study that found that fixing the CBV halved the width of the 95% CI.[11] This improvement can be explained by the fact that when the CBV is fixed to a value estimated by gamma-variate curve fitting, the information in the entire TAC is used instead of the steady state only. The finding that the average absolute Patlak $K^{trans}$ estimates were twice as high as the values measured with NLR and Patlak with fixed offset was also in line with the previous study, and can be explained by the fact that noise gives a positive bias to $K^{trans}$ estimates.



The discriminating power of the best predictor, rPS measured using NLR, although significant, is still on the low side with an area under the ROC curve of 0.75 (95% CI: 0.62 to 0.89) when measured in the infarct core. Furthermore, the 95% CIs on the AUCs are rather large due to the small population size. However, since multiple parameters showed significant discriminating power, multivariate analysis may result in a larger AUC. The additional value in predicting HT, compared to all perfusion parameters as well as clinical and demographic data, needs to be assessed by multivariate analysis in a larger stroke cohort.

The average infarct core size, as measured on admission CTP, was larger in the HT group, although not significantly. One may expect that the chance of developing HT increases with infarct size. However, this study showed that the average permeability values, measured in the infarct core, are better predictors for HT than the infarct core size.

A limitation of the study is that not all patients that developed HT received IVT treatment. We did not require IVT treatment for the patients in the HT group because those patients who showed HT on the follow-up scan without receiving treatment, would most probably also have developed HT if they did receive IVT treatment. In case IVT would be required for both groups, this would reduce the number of patients in the HT group. Since IVT is thought to increase the probability of developing HT, the five patients that did not receive IVT treatment in the HT group might have had higher permeability values and therefore might have increased the discrimination between the HT group and the non-HT group. However, this did not occur because for none of the measured parameters a significant difference between these subgroups was found, and the permeability values were on average even lower in the subgroup that did not receive IVT treatment.

Another limitation is that around 20% of the permeability maps showed ring-shaped scanner artifacts. These artifacts are positioned in the isocenter of the gantry and are the result of sub-optimal detector calibration.[29] Due to small differences in calibration, the CT-values in the images may have a variable offset and gain depending on the distance to the isocenter. This effect is especially dominant at low tube currents as used in CTP. When the time frames in a CTP scan are each rotated or translated to correct for patient motion, the displacement of these rings will introduce noise in the CT-values in the temporal dimension, to which the permeability maps are sensitive.

Furthermore, the data could be improved by enhancing the detector calibration and the use of a more sophisticated, iterative reconstruction technique. These improvements could increase the signal to noise ratio and reduce artifacts without increasing the radiation dose or reducing the resolution.

In contrast to many other studies that investigated BBB permeability in stroke, the baseline NIHSS scores in between the HT- and control group were not significantly different in this population.[30-35] This could be explained by the shorter median time to treatment (111 min versus 120 to 311 min for other studies).[6, 21, 30, 36–38] The fact that the clinical parameters between the groups in this study were similar endorses the presented results.



# Conclusions

The NLR method provides estimates for permeability parameters that are promising for predicting HT. The predictor rPS, measured in the infarct core, showed the highest discriminative power, while $rK^{trans}$, rCBF, and rMTT measured with NLR were also significantly stronger in the HT group than in the control group. This finding confirms the hypothesis that including the information in all data points of the attenuation curves is an important advantage of NLR over linearized regression. HT prediction using NLR might become a valuable addition to the existing CT stroke protocol in patients with acute ischemic stroke.

# References


1. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-1329
2. NINDS rssg. 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;333:1581-1587
3. Alvarez-Sabin J, Maisterra O, Santamarina E, Kase CS. Factors influencing haemorrhagic transformation in ischaemic stroke. Lancet Neurology. 2013;12:689-705
4. Wang X, Tsuji K, Lee SR, Ning M, Furie KL, Buchan AM, Lo EH. Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. Stroke. 2004;35:2726-2730
5. Bisdas S, Hartel M, Cheong LH, Koh TS, Vogl TJ. Prediction of subsequent hemorrhage in acute ischemic stroke using permeability CT imaging and a distributed parameter tracer kinetic model. J Neuroradiol. 2007;34:101-108
6. Dankbaar JW, Hom J, Schneider T, Cheng SC, Lau BC, van der Schaaf I, Virmani S, Pohlman S, Dillon WP, Wintermark M. Dynamic Perfusion CT Assessment of the Blood-Brain Barrier Permeability: First Pass versus Delayed Acquisition. AJNR Am J Neuroradiol. 2008;29:1671-1676
7. Lin K, Kazmi KS, Law M, Babb J, Peccerelli N, Pramanik BK. Measuring Elevated Microvascular Permeability and Predicting Hemorrhagic Transformation in Acute Ischemic Stroke Using First-Pass Dynamic Perfusion CT Imaging. AJNR Am J Neuroradiol. 2007;28:1292-1298
8. Larsson HB, Courivaud F, Rostrup E, Hansen AE. Measurement of brain perfusion, blood volume, and blood-brain barrier permeability, using dynamic contrast-enhanced T(1)-weighted MRI at 3 tesla. Magn Reson Med. 2009;62:1270-1281
9. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab. 1985;5:584-590
10. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab. 1983;3:1-7
11. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751
12. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37
13. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. Stroke.

1989;20:864-870

14. 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;32:1330-1335

15. 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. Lancet. 2000;355:1670-1674

16. Fahmi F, Riordan A, Beenen LF, Streekstra GJ, Janssen NY, de Jong HW, Majoie CB, van Bavel E, Marquering HA. The effect of head movement on CT perfusion summary maps: simulations with CT hybrid phantom data. Med Biol Eng Comput. 2013

17. Klein S, Staring M, Murphy K, Viergever MA, Pluim JP. elastix: a toolbox for intensity-based medical image registration. IEEE T Med Imaging. 2010;29:196-205

18. Mendrik AM, Vonken EJ, van Ginneken B, de Jong HW, Riordan A, van Seeters T, Smit EJ, Viergever MA, Prokop M. TIPS bilateral noise reduction in 4D CT perfusion scans produces high-quality cerebral blood flow maps. Phys Med Biol. 2011;56:3857-3872

19. Crone C. Facilitated transfer of glucose from blood into brain tissue. J Physiol. 1965;181:103-113

20. Renkin EM. Transport of potassium-42 from blood to tissue in isolated mammalian skeletal muscles. Am J Physiol. 1959;197:1205-1210

21. Schneider T, Hom J, Bredno J, Dankbaar JW, Cheng SC, Wintermark M. Delay Correction for the Assessment of Blood-Brain Barrier Permeability Using First-Pass Dynamic Perfusion CT. AJNR Am J Neuroradiol. 2010;32:E134-E138

22. Bivard A, Levi C, Spratt N, Parsons M. Perfusion CT in acute stroke: a comprehensive analysis of infarct and penumbra. Radiology. 2013;267:543-550

23. Nelder JA, Mead R. A simplex method for function minimization. The Computer Journal. 1965;7:308-313

24. Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical Recipes, 3rd Edition: The Art of Scientific Computing (Cambridge University Press, New York, NY, 2007).

25. Konstas AA, Goldmakher GV, Lee TY, Lev MH. Theoretic basis and technical implementations of CT perfusion in acute ischemic stroke, part 1: Theoretic basis. AJNR Am J Neuroradiol. 2009;30:662-668

26. Rempp KA, Brix G, Wenz F, Becker CR, Guckel F, Lorenz WJ. Quantification of regional cerebral blood flow and volume with dynamic susceptibility contrast-enhanced MR imaging. Radiology. 1994;193:637-641

27. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, Pineda C, Serena J, van der Schaaf I, Waaijer A, Anderson J, Nesbit G, Gabriely I, Medina V, Quiles A, Pohlman S, Quist M, Schnyder P, Bogousslavsky J, Dillon WP, Pedraza S. Perfusion-CT assessment of infarct

core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006;37:979-985

28. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, Hu WY, Buchan AM. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001;22:1534-1542

29. Barrett JF, Keat N. Artifacts in CT: recognition and avoidance. Radiographics. 2004;24:1679-1691

30. Aviv RI, d'Esterre CD, Murphy BD, Hopyan JJ, Buck B, Mallia G, Li V, Zhang L, Symons SP, Lee TY. Hemorrhagic transformation of ischemic stroke: prediction with CT perfusion. Radiology. 2009;250:867-877

31. Bang OY, Buck BH, Saver JL, Alger JR, Yoon SR, Starkman S, Ovbiagele B, Kim D, Ali LK, Sanossian N, Jahan R, Duckwiler GR, Viñuela F, Salamon N, Villablanca JP, Liebeskind DS. Prediction of hemorrhagic transformation after recanalization therapy using T2*-permeability magnetic resonance imaging. Annals of Neurology. 2007;62:170-176

32. Hjort N, Wu O, Ashkanian M, Solling C, Mouridsen K, Christensen S, Gyldensted C, Andersen G, Ostergaard L. MRI Detection of Early Blood-Brain Barrier Disruption: Parenchymal Enhancement Predicts Focal Hemorrhagic Transformation After Thrombolysis. Stroke. 2008;39:1025-1028

33. Kassner A, Roberts TPL, Moran B, Silver FL, Mikulis DJ. Recombinant Tissue Plasminogen Activator Increases Blood-Brain Barrier Disruption in Acute Ischemic Stroke: An MR Imaging Permeability Study. AJNR Am J Neuroradiol. 2009;30:1864-1869

34. Kim EY, Na DG, Kim SS, Lee KH, Ryoo JW, Kim HK. Prediction of hemorrhagic transformation in acute ischemic stroke: role of diffusion-weighted imaging and early parenchymal enhancement. AJNR Am J Neuroradiol. 2005;26:1050-1055

35. Latour LL, Kang DW, Ezzeddine MA, Chalela JA, Warach S. Early blood-brain barrier disruption in human focal brain ischemia. Ann Neurol. 2004;56:468-477

36. Dankbaar JW, Hom J, Schneider T, Cheng S-C, Lau BC, van der Schaaf I, Virmani S, Pohlman S, Dillon WP, Wintermark M. Accuracy and Anatomical Coverage of Perfusion CT Assessment of the Blood-Brain Barrier Permeability: One Bolus versus Two Boluses. Cerebrovasc Dis. 2008;26:600-605

37. Hom J, Dankbaar JW, Schneider T, Cheng SC, Bredno J, Wintermark M. Optimal Duration of Acquisition for Dynamic Perfusion CT Assessment of Blood-Brain Barrier Permeability Using the Patlak Model. AJNR Am J Neuroradiol. 2009;30:1366-1370

38. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, Lau BC, Smith W, Dillon WP, Wintermark M. Blood-Brain Barrier Permeability Assessed by Perfusion CT Predicts Symptomatic Hemorrhagic Transformation and Malignant Edema in Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2011;32:41-48

# CHAPTER 6

# Can blood-brain barrier CT perfusion derived permeability measurements predict hemorrhagic transformation in acute ischemic stroke?

Alexander D. Horsch, Edwin Bennink, Tom van Seeters, L. Jaap Kappelle, Yolanda van der Graaf, Willem P.Th.M. Mali, Hugo W.A.M. de Jong, Birgitta K. Velthuis, Jan Willem Dankbaar, on behalf of the DUST investigators

Submitted

# Abstract

## Background

Hemorrhagic transformation (HT) in acute ischemic stroke can occur as a result of reperfusion treatment. Although withholding treatment may be warranted in patients with increased risk of HT, prediction of HT remains difficult. Nonlinear regression permeability is a new technique to estimate blood-brain barrier permeability (BBBP). The aim of this study was to identify a combination of variables that predict HT and assess the added value of BBBP.

## Methods

From the Dutch acute stroke study (DUST) 545 patients treated with intra-venous recombinant tissue Plasminogen Activator (IV-rtPA) and/or intra-arterial treatment were selected, with available admission extended CT perfusion and follow-up imaging. Patient admission treatment characteristics and CT imaging parameters regarding occlusion site, stroke severity and BBBP were recorded. HT was assessed on day 3 follow-up imaging. The association between potential predictors and HT was analyzed using univariate and multivariate logistic regression. To compare the added value of BBBP area under the curve's (AUC) were created from two models, with and without BBBP.

## Results

HT developed in 57 patients (10%). In univariate analysis, older age (odds ratio (OR) 1.03, 95% CI 1.006-1.05), higher admission National Institutes of Health Stroke Scale (NIHSS) (OR 1.13, 95% CI 1.08-1.18), higher clot burden (OR 1.28, 95% CI 1.16-1.41), poor collateral score (OR 3.49, 95% CI 1.85-6.58), larger Alberta Stroke Program Early CT Score (ASPECTS) cerebral blood volume (CBV) deficit size (OR 1.26, 95% CI 1.14-1.38) and increased BBBP (OR 2.22, 95% CI 1.46-3.37) were associated with HT. In multivariate analysis with age and admission NIHSS, the addition of BBBP did not improve the AUC compared to both independent predictors alone (AUC 0.77, 95% CI 0.71-0.83).

## Conclusion

BBBP predicts HT but does not improve prediction with age and admission NIHSS.

# Introduction

Hemorrhagic transformation (HT) is a serious complication of acute ischemic stroke. Larger parenchymal HT can cause death or severe disability, but smaller HT also have been related to worse outcome.[1, 2] In clinical practice, with intra-venous rtPA treatment (IV-rtPA) given within 3 hours, HT occurs in 12% of cases.[3] In some clinical trials higher incidences (up to 40%) were found, with rates depending on patient selection, time to treatment, definition of HT and time to follow-up.[4-7] In patients treated with IV-rtPA and subsequent HT, mortality can be as high as 9% (with symptomatic HT) and morbidity up to 50%.[1, 8]

Risk factors for HT have been investigated in a recent meta-analysis and include higher age and higher stroke severity.[9] Several scores can help predict HT, but none has achieved widespread use in clinical practice.[10-12] The meta-analysis and most of these scores do not incorporate information from CT angiography (CTA) and CT perfusion (CTP) imaging. Several CT imaging parameters related to the ischemic lesion, have been associated with an increased risk of HT: large vessel occlusion and collateral score on CTA and infarct core volume and ischemic lesion volume on CTP.[13-17]

Disturbance of the blood-brain barrier (BBB) has been implicated in HT occurrence and can be measured with CT perfusion.[18-21] However, none of the papers assessing BBB permeability (BBBP) were included in the recent meta-analysis.[9, 18-21] The Patlak model is the most frequently used model to described BBBP but only considers unidirectional flow.[22] Other models to describe BBBP, like nonlinear regression (NLR) have demonstrated to be more reliable and robust in estimating BBBP.[23] Prediction of HT may therefore also improve by using this method, as previously has been shown in a small group of patients.[24]

The aim of this study was to assess the added value of BBBP measurements to known clinical and imaging variables that predict the risk of HT.



# Materials and methods

## Study design

Patients were included from the prospective multicenter Dutch acute stroke study (DUST), which aims to assess the additional value of CT perfusion (CTP) and CT angiography (CTA) in predicting outcome of acute ischemic stroke patients.[25, 26] Adult patients were included with a clinical diagnosis of acute ischemic stroke, with a National Institutes of Health Stroke Scale (NIHSS) of ≥2, or 1 if an indication for IV-rtPA was present.[25, 26] This study was approved by the local institutional ethical review boards of the participating centers. All patients or family

gave signed informed consent, unless a patient died before consent could be obtained. In that case the medical ethics committee waived the need for consent.[25, 26]

## Patient selection

From the DUST study database, with patient inclusion between May 2009 and August 2013, we selected all patients treated with IV-rtPA and/or intra-arterial treatment (thrombolysis or mechanical thrombectomy), a good quality extended CT perfusion on admission and available follow-up imaging. We collected clinical data on age, sex, history of stroke, diabetes, atrial fibrillation, myocardial infarction, or hypertension, admission NIHSS, treatment with IV-rtPA and/or intra-arterial treatment. The inclusion process is clarified in the flow chart (Figure 1).

## Image protocol

All patients underwent non-contrast CT (NCCT) and CTP of the brain and CTA of the cervical and cerebral vessels on admission. Follow-up NCCT (in small minority MRI) was done at 3 days (+/- 2 days) or earlier in case of clinical deterioration. Reasons for no follow-up imaging were: no permission for follow-up, or poor condition of the patient, or very rapid recovery and discharge within 24 hours before follow-up could be done. Scan protocols and parameters have been described in detail previously.[25, 26]

## Image analysis

All imaging data were evaluated by one of three observers (I.C.vdS, B.K.V. and J.W.D), all with at least 5 years of experience in stroke imaging. Only the side of symptoms was provided for the evaluation.

NCCT: On the follow-up scan HT was classified according to the radiological European Cooperative Acute Stroke Study (ECASS) criteria only, because HT related symptomatology was not rigorously collected.[27]

CTP: Cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT)

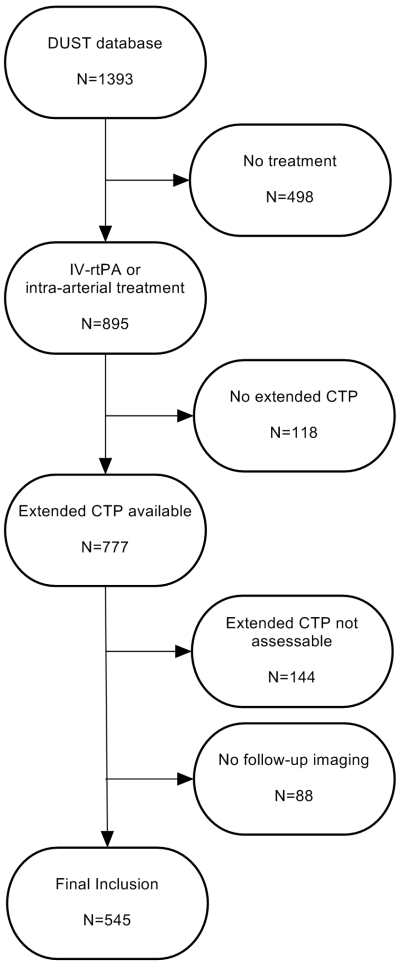



Figure 1. Flow chart 1 patient selection.

and time to peak (TTP) were automatically calculated from CTP data utilizing commercially available CTP software (Extended Brilliance Workstation 4.5, Philips Healthcare). Presence of a perfusion deficit on admission was defined as a focal asymmetry on the MTT, CBF or CBV map matching a part or the whole of the MCA flow territory. The infarct core was evaluated on CBV maps and classified with Alberta Stroke Program Early CT Score (ASPECTS).[28]

A nonlinear regression (NLR) method, employing a mathematical tissue response model to describe an impulse response function obtained from the extended acquisition, was used to estimate the BBBP surface area (PS). PS was calculated relative to the non-affected hemisphere.[23] This measurement is referred to as BBBP in this study.

CTA: Admission CTA provided data on clot burden score (CBS) and collateral score. These scoring systems have been described in detail previously.[14, 29, 30]

### Statistical analysis

Patient characteristics and imaging data were presented as numbers with percentages, means with SD or medians with IQ. Missing values occurred in some variables and were substituted with single imputation. The association between variables and HT was analyzed using univariate and multivariate regression analysis. Because we had only a limited number of outcomes, only 6 variables could be selected maximally to have 10 outcomes per variable. All selected variables are known predictors of HT found in literature.[9] Variables analyzed were age, admission NIHSS, CBS (0-10), collateral score (good or poor), decreased CBV (ASPECTS 0-10), and NLR BBBP values. Statistical computations were carried out using SPSS 23.0 (IBM corporation, NY, USA).



## Results

From the 1393 patients included in the DUST study, 895 (64.2%) received IV-rtPA or intra-arterial treatment (Figure 1). Of these, 777 had an extended CTP and this was usable in 633 cases. The main reason for unusable extended CTP was the sensitivity of the BBBP measurement pre- and post-processing techniques to patient movements. In the final inclusion remained 545 patients who also had available follow-up imaging (CT 92% and MRI 8%). On follow-up HT was found in 57 cases (10%). ECASS types were: 12 hemorhagic infarction-1 (HI-1) (21%), 17 HI-2 (30%), 15 parenchymal hemorrhage-1 (PH-1) (26%) and 13 PH-2 (23%) (Table 1). The percentage HT in all patients with follow-up imaging in the DUST study was comparable (11%).

In univariate analysis (Table 2) older age, higher NIHSS, higher clot burden, poor collateral score, larger ASPECTS CBV deficit size and increased BBBP were all associated with HT.

**Table 1. Clinical and imaging characteristics.**

| | All patients N=545 | HT patients N=57 | No HT patients N=488 | P-value |
|---|---|---|---|---|
| **Clinical parameters** | | | | |
| Age, median (IQ) | 68 (58-77) | 71 (65-81) | 67 (57-76) | 0.10* |
| Female sex, n (% ) | 214 (39) | 22 (39) | 192 (39) | 0.91 |
| History of stroke, n (%) | 122 (22) | 16 (28) | 106 (22) | 0.28 |
| History of diabetes, n (%) | 73 (13) | 7 (12) | 66 (14) | 0.79 |
| History of atrial fibrillation, n (%) | 56 (10) | 10 (18) | 46 (9) | 0.56 |
| History of myocardial infarction, n (%) | 68 (13) | 9 (16) | 59 (12) | 0.42 |
| History of hypertension, n (%) | 280 (51) | 34 (60) | 246 (50) | 0.19 |
| NIHSS, median (IQ) | 8 (4-13) | 13 (9-19) | 7 (4-12) | 0.0001* |
| IAT and/or MT, n (%) | 44 (8) | 9 (16) | 35 (7) | 0.02* |
| **Imaging parameters** | | | | |
| Time to scan, minutes, median (IQ) | 89 (64-135) | 85 (58-135) | 90 (65-135) | 0.19 |
| **Admission CT angiography** | | | | |
| Clot burden score (0-10), median, (IQ) | 10 (8-10) | 8 (5-10) | 10 (8-10) | 0.0001* |
| Poor collateral score, n (%) | 70 (13) | 17 (30) | 53 (11) | 0.00005* |
| **Admission CT perfusion** | | | | |
| Size CBV deficit, ASPECTS, median, (IQ) | 10 (8-10) | 8 (5-10) | 10 (8-10) | 0.0001* |
| NLR Permeability ratio (BBBP), median (IQ) | 1.07 (0.96-1.29) | 1.31 (1.01-1.60) | 1.06 (0.95-1.26) | 0.001* |
| **Follow-up non-contrast CT** | | | | |
| All HT, n (%) | 57 (10) | 57 (100) | N/A | N/A |
| PH-2, n (%) | 13 (2) | 13 (23) | N/A | N/A |

Chi-squared test was used to compare categorical variables and Mann-Whitney U test for continuous variables.
* All $p<0.05$
ASPECTS, Alberta Stroke Program Early CT score; BBBP, blood-brain permeability; CBV, cerebral blood volume; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; HT, hemorrhagic transformation; IAT, intra-arterial thrombolysis; IV-rtPA, intra-venous recombinant tissue Plasminogen Activator; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; NLR, nonlinear regression; MT, mechanical thrombectomy; PH, parenchymal hemorrhage.

**Table 2. Univariate and multivariate analysis for BBBP and other predictors of HT in patients treated with IV-rtPA or intra-arterial treatment (n=545).**

| | Univariate | | Multivariate without BBBP | | Multivariate with BBBP | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** |
| **Clinical parameters** | | | | | | |
| Age, per year | 1.03 | 1.006-1.05* | 1.03 | 1.003-1.05* | 1.03 | 1.002-1.05* |
| NIHSS, per point | 1.13 | 1.08-1.18* | 1.09 | 1.04-1.15* | 1.09 | 1.04-1.15* |
| **Imaging parameters** | | | | | | |
| Clot burden score (0-10) | 1.28 | 1.16-1.41* | 1.10 | 0.94-1.27 | 1.09 | 0.93-1.27 |
| Poor collateral score | 3.49 | 1.85-6.58* | 1.32 | 0.62-2.81 | 1.30 | 0.61-2.78 |
| Size CBV deficit, ASPECTS | 1.26 | 1.14-1.38* | 1.04 | 0.90-1.20 | 1.03 | 0.88-1.19 |
| NLR Permeability ratio (BBBP) | 2.22 | 1.46-3.37* | N/A | N/A | 1.20 | 0.72-2.02 |

See legend Table 1.

In a multivariate analysis with all selected variables remaining in the model, only age and NIHSS were independent predictors of HT (area under the curve (AUC): 0.77, 95%CI 0.71-0.83). The addition of BBBP as a variable did not change the AUC (0.77, 95%CI 0.71-0.83) of the model.

In additional univariate analysis, the relation between BBBP and PH-2 type HT was not

significant (but based on only 13 outcomes). In a sub-analysis of patients with a proven intra-cranial arterial occlusion on admission CTA (n=299), BBBP was neither significantly associated with PH-2 type HT in univariate analysis, nor did it add to prediction of all types of HT with age and admission NIHSS in multivariate analysis.

# Discussion

The main finding of this study is that nonlinear BBBP can predict HT in acute ischemic stroke. However, BBBP has no additional predictive value in combination with other predictors, like age and admission NIHSS.

The maximum AUC for predicting HT found in our study was relatively low at 0.77, but was within the range of the results of other multivariate analyses in studies investigating predictors of HT with CTP (range: 0.69 to 0.92).[13, 16, 17, 19, 31] Three studies found higher AUCs. Jain 2013 found an AUC of 0.83 for relative CBV with a cut-off point of 1.09, Lin 2012 found a AUC of 0.89 for predicting sICH with ASPECTS, and Aviv 2009 found an AUC of 0.92 for permeability-surface area product. We did find a significant relation between CBV deficit and permeability, and the occurrence of HT in univariate analysis, but this could not be confirmed in our multivariate analysis. We chose not to use admission NCCT variables in our study because the number of variables we could use was limited by the number of outcomes.

Several papers also describe a predictive value of BBBP measurements.[19-21, 32, 33] The acquisition and post processing techniques of assessing BBBP is different in all papers, which makes direct comparison difficult. Although all these studies showed a positive association between BBBP and HT, the studies were small (between 23 and 86 patients) with, as a consequence, a low number of outcomes. The percentage of HTs between studies showed a large variation (12 to 56%, depending on further selection), while percentages in daily practice are typically at the lower end of this range.[3] This might have caused an important selection bias, which makes the results less applicable for clinical use. Moreover, the duration of the CTP acquisition in most was relatively short (50 to 135 seconds), which makes it questionable if they were truly measuring BBBP. Our study, with prospective inclusion of much larger number of patients suspected of acute ischemic stroke, uses a more robust bidirectional model (obtained from CTP acquisitions extended to 210 seconds), to assess BBBP. The number of HTs in our study is also much larger than in all other studies (57 versus 3 to 27).

Most of the variables used to predict HT relate to a large area of the brain. It is probably difficult to predict HT with those parameters as HT originates in a small area of the infarct, of which the location is difficult to determine in advance. The averaging with the normal values in the surrounding area could obscure higher values in this small area. Measurement of BBBP remains complex due to the inherent problems with the low contrast to noise ratio in an ischemic area and movement artifacts on the extended CTP. The images are quite

difficult to interpret and the differentiation between focal abnormalities and artifacts proves challenging, relying on thresholds or comparison of brain areas or hemispheres. Prediction with BBBP could be improved by enhancing detector calibration to reduce the ring shaped scanner artifacts which are a cause of noise, and the use of more sophisticated iterative reconstruction techniques to reduce artifacts and increase the signal to noise ratio.[24]

Strengths of this study are the prospective inclusion of a large population of suspected ischemic stroke patients analysed with BBBP and the combined use of clinical, NCCT, CTA and CTP parameters.

This study also has limitations. First, the number of exclusions due to technical processing difficulties with an extended CTP was rather high (19%), but this could be reduced by techniques described above. As the percentage and types of HT are comparable in all DUST patients with follow-up imaging, it is unlikely that this has changed our results.

Second, the number of PH-2 type HT in our population was too small for sub-analysis. This is unfortunate, as PH-2 is a major determinant of poor outcome. However, smaller HTs have also been implicated in worse longer term clinical outcome.[1, 2] This means our results are not directly transferable to the PH-2 population in particular, but nonetheless important for HT prediction in general.

Third, a small percentage of follow-up was performed with MRI instead of CT imaging. It is known that MRI is more sensitive in detecting smaller HT.[34] In contrast, the percentage of smaller HT (HI-1 and HI-2) in our population was not higher in patients with MRI follow-up compared to patients with CT follow-up, which makes bias due to a difference in modalities unlikely.



# Conclusions

Nonlinear blood-brain barrier BBBP measurements are related to the occurrence of HT in acute ischemic stroke, but do not improve prediction of HT with age and admission NIHSS. The technique of BBBP measurements requires further improvement before it can be a useful addition to decision making in patients considered for IV-rtPA treatment.

# References


1. Park JH, Ko Y, Kim WJ, Jang MS, Yang MH, Han MK, Oh CW, Park SH, Lee J, Bae HJ, Gorelick PB. Is asymptomatic hemorrhagic transformation really innocuous? Neurology. 2012;78:421-426
2. Kimura K, Iguchi Y, Shibazaki K, Aoki J, Terasawa Y. Hemorrhagic transformation of ischemic brain tissue after t-PA thrombolysis as detected by MRI may be asymptomatic, but impair neurological recovery. J Neurol Sci. 2008;272:136-142
3. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke. 2003;34:2847-2850
4. Terruso V, D'Amelio M, Di Benedetto N, Lupo I, Saia V, Famoso G, Mazzola MA, Aridon P, Sarno C, Ragonese P, Savettieri G. Frequency and determinants for hemorrhagic transformation of cerebral infarction. Neuroepidemiology. 2009;33:261-265
5. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275-282
6. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375:1695-1703
7. Sussman ES, Connolly ES, Jr. Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol. 2013;4:69
8. Strbian D, Sairanen T, Meretoja A, Pitkaniemi J, Putaala J, Salonen O, Silvennoinen H, Kaste M, Tatlisumak T. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. Neurology. 2011;77:341-348
9. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke. 2012;43:2904-2909
10. Strbian D, Engelter S, Michel P, Meretoja A, Sekoranja L, Ahlhelm FJ, Mustanoja S, Kuzmanovic I, Sairanen T, Forss N, Cordier M, Lyrer P, Kaste M, Tatlisumak T. Symptomatic intracranial hemorrhage after stroke thrombolysis: The SEDAN Score. Ann Neurol. 2012;71:634-641
11. Lou M, Safdar A, Mehdiratta M, Kumar S, Schlaug G, Caplan L, Searls D, Selim M. The HAT Score: A simple grading scale for predicting hemorrhage after thrombolysis. Neurology. 2008;71:1417-1423
12. Cucchiara B, Tanne D, Levine SR, Demchuk AM, Kasner S. A risk score to predict intracranial hemorrhage after recombinant tissue plasminogen activator for acute ischemic stroke. J Stroke Cerebrovasc Dis. 2008;17:331-333

13. Lin K, Zink WE, Tsiouris AJ, John M, Tekchandani L, Sanelli PC. Risk Assessment of Hemorrhagic Transformation of Acute Middle Cerebral Artery Stroke Using Multimodal CT. J Neuroimaging. 2012;22:160-166

14. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, O'Reilly C, Hudon ME, Hu WY, Coutts SB, Barber PA, Watson T, Roy J, Demchuk AM. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3:230-236

15. Fanou EM, Knight J, Aviv RI, Hojjat SP, Symons SP, Zhang L, Wintermark M. Effect of Collaterals on Clinical Presentation, Baseline Imaging, Complications, and Outcome in Acute Stroke. AJNR Am J Neuroradiol. 2015;36:2285-2291

16. Jain AR, Jain M, Kanthala AR, Damania D, Stead LG, Wang HZ, Jahromi BS. Association of CT perfusion parameters with hemorrhagic transformation in acute ischemic stroke. AJNR Am J Neuroradiol. 2013;34:1895-1900

17. Souza LC, Payabvash S, Wang Y, Kamalian S, Schaefer P, Gonzalez RG, Furie KL, Lev MH. Admission CT Perfusion Is an Independent Predictor of Hemorrhagic Transformation in Acute Stroke with Similar Accuracy to DWI. Cerebrovasc Dis. 2012;33:8-15

18. Bektas H, Wu TC, Kasam M, Harun N, Sitton CW, Grotta JC, Savitz SI. Increased blood-brain barrier permeability on perfusion CT might predict malignant middle cerebral artery infarction. Stroke. 2010;41:2539-2544

19. Aviv RI, d'Esterre CD, Murphy BD, Hopyan JJ, Buck B, Mallia G, Li V, Zhang L, Symons SP, Lee TY. Hemorrhagic transformation of ischemic stroke: prediction with CT perfusion. Radiology. 2009;250:867-877

20. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, Lau BC, Smith W, Dillon WP, Wintermark M. Blood-Brain Barrier Permeability Assessed by Perfusion CT Predicts Symptomatic Hemorrhagic Transformation and Malignant Edema in Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2011;32:41-48

21. Ozkul-Wermester O, Guegan-Massardier E, Triquenot A, Borden A, Perot G, Gerardin E. Increased blood-brain barrier permeability on perfusion computed tomography predicts hemorrhagic transformation in acute ischemic stroke. Eur Neurol. 2014;72:45-53

22. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab. 1983;3:1-7

23. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751

24. Bennink E, Horsch AD, Dankbaar JW, Velthuis BK, Viergever MA, de Jong HW. CT perfusion analysis by nonlinear regression for predicting hemorrhagic transformation in ischemic stroke. Medical physics. 2015;42:4610-4618

25. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37

26. van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Niesten JM, Luitse MJ, Majoie CB, Vos JA, Schonewille WJ, van Walderveen MA, Wermer MJ, Duijm LE, Keizer K, Bot JC, Visser MC, van der Lugt A, Dippel DW, Kesselring FO, Hofmeijer J, Lycklama ANGJ, Boiten J, van Rooij WJ, de Kort PL, Roos YB, van Dijk EJ, Pleiter CC, Mali WP, van der Graaf Y, Velthuis BK. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc Dis. 2015;40:258-269

27. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025

28. van Seeters T, Biessels GJ, Niesten JM, van der Schaaf IC, Dankbaar JW, Horsch AD, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Reliability of Visual Assessment of Non-Contrast CT, CT Angiography Source Images and CT Perfusion in Patients with Suspected Ischemic Stroke. PLoS One. 2013;8:e75615

29. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. AJNR Am J Neuroradiol. 2009;30:525-531

30. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61:533-543

31. Yassi N, Parsons MW, Christensen S, Sharma G, Bivard A, Donnan GA, Levi CR, Desmond PM, Davis SM, Campbell BC. Prediction of Poststroke Hemorrhagic Transformation Using Computed Tomography Perfusion. Stroke. 2013

32. Lin K, Kazmi KS, Law M, Babb J, Peccerelli N, Pramanik BK. Measuring Elevated Microvascular Permeability and Predicting Hemorrhagic Transformation in Acute Ischemic Stroke Using First-Pass Dynamic Perfusion CT Imaging. AJNR Am J Neuroradiol. 2007;28:1292-1298

33. Bisdas S, Hartel M, Cheong LH, Koh TS, Vogl TJ. Prediction of subsequent hemorrhage in acute ischemic stroke using permeability CT imaging and a distributed parameter tracer kinetic model. J Neuroradiol. 2007;34:101-108

34. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, Butman JA, Patronas N, Alger JR, Latour LL, Luby ML, Baird AE, Leary MC, Tremwel M, Ovbiagele B, Fredieu A, Suzuki S, Villablanca JP, Davis S, Dunn B, Todd JW, Ezzeddine MA, Haymore J, Lynch JK, Davis L, Warach S. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA. 2004;292:1823-1830

# CHAPTER 7

# Imaging Findings Associated with Space-Occupying Edema in Patients with Large Middle Cerebral Artery Infarcts

Alexander D. Horsch, Jan Willem Dankbaar, Tom A. Stemerdink, Edwin Bennink, Tom van Seeters, L. Jaap Kappelle, Jeannette Hofmeijer, Hugo W.A.M. de Jong, Yolanda van der Graaf, and Birgitta K. Velthuis; on behalf of the DUST investigators

Adapted from:
**AJNR Am J Neuroradiol. 2016 May;37(5):831-7**

# Abstract

## Background

Prominent space-occupying cerebral edema is a devastating complication occurring in some but not all patients with large middle cerebral artery (MCA) infarcts. It is unclear why differences in extent of edema exist. Better knowledge of factors related to prominent edema formation could aid treatment strategies. This study aims to identify variables associated with development of prominent edema in patients with large MCA infarcts.

## Methods

From the Dutch acute stroke study (DUST), 137 patients were selected with large MCA infarcts on follow-up non-contrast CT (NCCT) (3 +/- 2 days after stroke onset), defined as Alberta Stroke Program Early CT Score (ASPECTS) ≤4. Prominent edema was defined as midline shift ≥5 mm on follow-up. Admission patient and treatment characteristics were collected. Admission CT parameters used were: ASPECTS on NCCT and cerebral blood volume (CBV) and mean transit time (MTT) maps, and occlusion site, clot burden, and collaterals on CT angiography (CTA). Permeability on admission CT perfusion (CTP), and day 3 recanalization and reperfusion status were obtained if available. Unadjusted and adjusted (for age and National Institutes of Health Stroke Scale, NIHSS) odds ratios were calculated for all variables in relation to prominent edema.

## Results

Prominent edema developed in 51 patients (37%). Adjusted odds ratios (aOR) for prominent edema were higher with lower ASPECTS on NCCT (aOR 1.32, 95% CI 1.13-1.55) and CBV (aOR 1.26, 95% CI 1.07-1.49), higher permeability (aOR 2.35, 95% CI 1.30-4.24), more proximal thrombus location (aOR 3.40 95% CI 1.57-7.37), higher clot burden (aOR 2.88, 95% CI 1.11-7.45), and poor collaterals (aOR 3.93, 95% CI 1.78-8.69).

## Conclusion

Extensive proximal occlusion, poor collaterals, and larger ischemic deficits with higher permeability, play a role in the development of prominent edema in large MCA infarcts.

# Introduction

Prominent space-occupying edema can occur after acute large middle cerebral artery (MCA) ischemic stroke. The prominent space-occupying edema can cause herniation, increased intra-cranial pressure, and rapid neurological deterioration. This occurs in approximately 8% of MCA infarcts and has mortality of up to 80% with conservative treatment.[1-3] Current treatment options are limited; the only treatment of proven value is large hemicraniectomy within 48 hours after stroke onset.[4-6] The results from the hemicraniectomy trials showed a large decrease in mortality but with an increase in number of patients with severe disability.[4]

Although risk factors for prominent space-occupying edema have been identified, it is still unclear why only some patients with a large MCA infarct on follow-up develop prominent space-occupying edema.[7] Identification of associated variables is important to identify possible new targets for treatment development.[8]

The extent of the disturbance of the blood-brain barrier (BBB) may play a role in the development of prominent space-occupying edema.[9] A measure of the BBB permeability is the permeability surface area product, which can be obtained from an extended CT perfusion (CTP) acquisition.[10] Other known risk factors for prominent space-occupying edema development include proximal occlusion site, greater infarct size, involvement of more than one vascular territory, basal ganglia involvement, increased ratio of cerebral blood volume (CBV) lesion volume/cerebrospinal fluid (CSF) volume, female sex, and higher National Institutes of Health Stroke Scale (NIHSS) on admission.[9, 11-14]

The aim of this study was to identify clinical and CT imaging variables that are associated with the development of prominent space-occupying edema in patients with large MCA infarcts on follow-up.



# Materials and methods

## Patient selection

All patients participated in the Dutch acute stroke study (DUST), and the study protocol has been published previously.[15] Patients were included in the DUST study if they had a non-contrast CT (NCCT), CT angiography (CTA) and CTP within 9 hours after stroke onset. The local medical ethics committees of the participating centers approved this study. All patients or family gave signed informed consent, unless a patient died before consent could be obtained, in that case the need for consent was waived by the medical ethics committee.[15]

For the current study, patients were selected with a large infarct in the MCA territory defined as Alberta Stroke Program Early CT Score (ASPECTS) ≤4 on a follow-up NCCT, performed

3 (+/-2) days after stroke onset.[16] Exclusion criteria were hemorrhagic transformation with significant mass effect (European Cooperative Acute Stroke Study (ECASS) parenchymal hemorrhage type-2 (PH-2)), and poor quality admission CTP.[17] The selection process is clarified in the flow chart (Figure 1). We collected clinical data on age, sex, history of stroke or atrial fibrillation, admission NIHSS, IV-recombinant tissue Plasminogen Activator (IV-rtPA) treatment, intra-arterial treatment, and time from symptom onset to admission CT.

## Imaging protocol

NCCT and CTP of the brain, and CTA of the cervical and cerebral arteries were performed on admission. Follow-up NCCT was planned at 3 days (+/- 2) days and also performed in case of clinical deterioration. Additional follow-up CTA and CTP were also done if possible. Multi-detector CT scanners were used with number of detectors ranging from 40 to 320 (GE, Philips, Siemens, Toshiba). NCCT was performed with 120 kV, 300-375 mAs, and slice thickness of 5 mm.

The CTP, performed before CTA, was acquired with 80 kV and 150 mAs per rotation, and slice thickness of 5 mm, involved successive gantry rotations in cine mode (every 2 seconds for 50 seconds and 6 additional rotations 30 seconds apart) during intra-venous administration of 40 ml non-ionic contrast material followed by 40 ml of saline with a flow of 6 ml/s. CTP coverage included at least the level of the basal ganglia to the lateral ventricles to be able to assess both ASPECTS levels.[16] Mean transit time (MTT) and CBV maps were classified only with ASPECTS levels to ensure uniform assessment on all CTP scans was done, despite differences in scan range (40-320 slices).

The CTA was acquired from aortic arch to the vertex with 50-70 ml contrast followed by 40 ml of saline, with a flow of 6 ml/s. The individual CTA scan delay after intra-venous injection was calculated from time to peak arterial enhancement on CTP, or by trigger-based Hounsfield threshold measurement of contrast enhancement in the aortic arch.

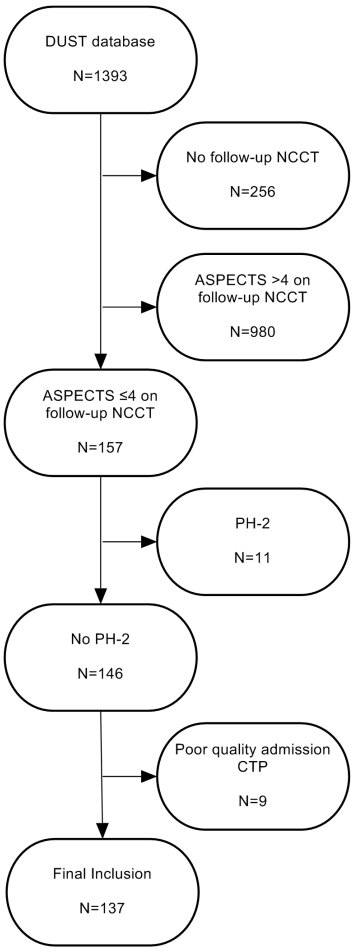



Figure 1. Inclusion flow chart.

## Imaging analysis

NCCT: On the admission scan we evaluated the ASPECTS score to quantify the presence of early CT signs of infarction.[16] On day 3 (+/-2) days follow-up the infarct size was classified with ASPECTS and the presence of prominent space-occupying edema was defined as a midline shift of ≥5 mm (see Figure 2).[11, 18, 19] Any hemorrhagic transformation on the follow-up scan was classified according to the ECASS criteria to identify patients with a PH-2 (hemorrhage >30% of infarcted area with significant space-occupying effect) as the midline shift in those patients is considered to be secondary to the large hemorrhage.[17]

CTP: cerebral blood volume (CBF), CBV, MTT, and time to peak (TTP) were automatically calculated from CTP data utilizing commercially available CTP software (Extended Brilliance Workstation 4.5, Philips Healthcare). Presence of a perfusion deficit on admission was defined as a focal asymmetry on the CBF, CBV or MTT map matching a part of or the complete MCA flow territory. MTT and CBV maps were classified with ASPECTS.[20] Involvement of the lentiform nucleus and additional anterior cerebral artery (ACA) vascular territory

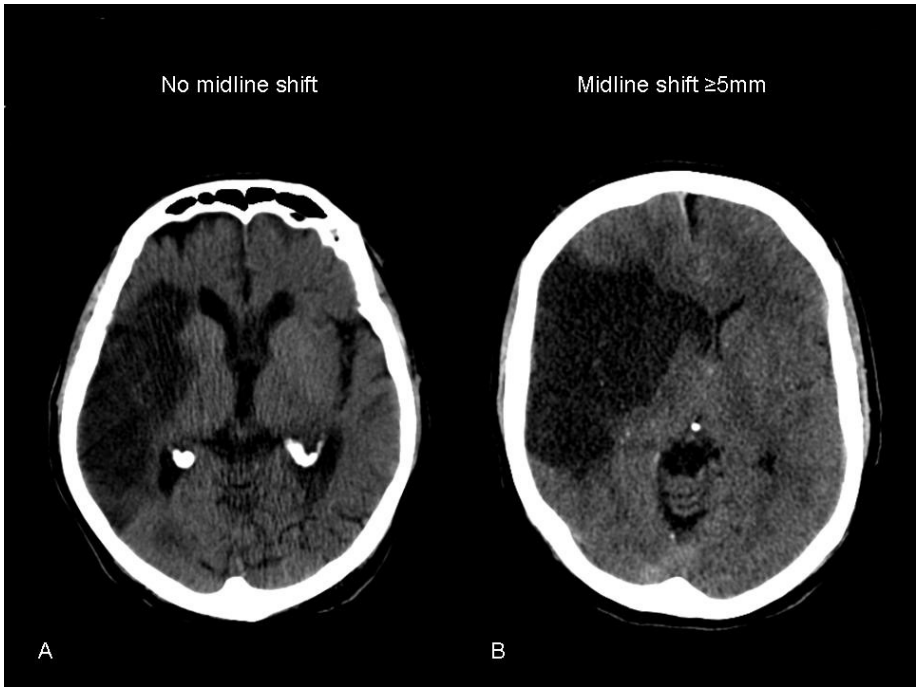



Figure 2. Large MCA infarct on follow-up, with and without prominent space-occupying edema. Patient A (87 year old male, follow-up day 5) has a large MCA infarct and generalized atrophy but does not show midline shift. Patient B (58 year old male, follow-up day 3) shows a large MCA infarct with a midline shift of ≥5mm, representing prominent space-occupying edema.

(including the caudate nucleus) were also evaluated separately.[11, 21] Reperfusion was evaluated quantitatively by assessment of the change in MTT abnormality (Soares et al. Stroke 2010), and categorized into a reperfusion and a no reperfusion group. Reperfusion was defined as resolution of 75% or more of the abnormality on the MTT maps comparing admission and follow-up CTP.[22]

To estimate the permeability surface area a nonlinear method, employing a mathematical response model to describe an impulse response function obtained from extended acquisition, was used. The permeability surface area was calculated relative to the non-affected hemisphere.[10]

CTA: Admission CTA provided data on intra-cranial thrombus location, clot burden score, and collateral score.[23-25] Thrombus location was classified to the most proximal site of occlusion unless there was a combined extra-cranial internal carotid artery (ICA) occlusion and a more distal MCA occlusion with an open ICA top (tandem lesion), which was classified at the level of the MCA occlusion (proximal flow maintained through Circle of Willis collaterals).[26] The clot burden score was obtained by evaluating the anterior circulation to the symptomatic hemisphere and subtracting segments with absent contrast opacification from the maximum score of 10, with 10 representing complete absence of any thrombus, and 0 a complete occlusion of all the segments. The score assigns 1 point to the infraclinoid ICA, to the ACA and to each M2 branch (with a maximum of 2), and 2 points to the supraclinoid part of the ICA and the proximal and distal part of the M1 segment.[23] The collateral score of the symptomatic hemisphere was evaluated by visual assessment of MIP images and the scoring system applied by Tan et al. AJNR 2009.[24] Leptomeningeal collaterals were graded on admission CTA by the extent of collateral filling in the MCA territory of the affected hemisphere in comparison to the contra-lateral side: 0 = absent; 1 = filling ≤ 50%; 2 = filling 50-<100%; 3 = filling 100%. For analysis the scores were dichotomized in poor collaterals (0-1) and good collaterals (2-3). Tan et al. found a very good inter-observer correlation of 0.87 for this scoring system. Recanalization was evaluated by comparing admission and follow-up CTA, and defined qualitatively as recanalization or no recanalization. This compares to a thrombolysis in cerebral infarction (TICI) score of 0-2a for the no recanalization group and a TICI score of 2b or 3 for the recanalization group.[27]

All imaging data were collected and evaluated centrally by one of three observers (I.C.vdS, B.K.V. and J.W.D), all with at least 5 years of experience in stroke imaging. Only the side of symptoms was provided for the evaluation.

## Statistical analysis

For all analyses patients with prominent space-occupying edema were compared with patients without prominent space-occupying edema. The clinical variables were age, sex,

history of stroke, history of atrial fibrillation, admission NIHSS, IV-rtPA treatment or intra-arterial treatment, and time to admission scan series. Imaging variables were: early CT signs of infarction (ASPECTS 0-10), decreased CBV (ASPECTS 0-10), prolonged MTT (ASPECTS 0-10), presence of decreased CBV in lentiform nucleus (yes/no), presence of decreased CBV in caudate nucleus and/or ACA vascular territory (yes/no), clot burden score (cutoff ≤6), thrombus location (ICA/proximal M1 versus distal M1, M2 or >M2), and collateral score (good or poor).[24] Permeability estimates, recanalization (recanalization versus no recanalization) and reperfusion (reperfusion versus no reperfusion) were analyzed in a sub-analysis because these data were not available in all patients.

To compare variables, chi-squared test, t-test, or Mann-Whitney U test were used. The association between variables and prominent space-occupying edema was analyzed using univariate and multivariate regression. Odds ratios were adjusted for age and admission NIHSS (aOR) with multivariate logistic regression. Significance was pre-defined at $p<0.05$. Statistical computations were carried out using SPSS 23.0 (IBM corporation, NY, USA).

# Results

Inclusion criteria for this study were met in 137 patients. Not all patients in the DUST study received follow-up imaging. Main reasons for this were: no permission for follow-up, no follow-up due to discharge within 24 hours in patients with rapid recovery, poor condition

**Table 1. Clinical and imaging characteristics.**

| | All patients N=137 | Prominent space-occupying edema N=51 | No prominent space-occupying edema N=86 | P-value |
|---|---|---|---|---|
| **Clinical parameters** | | | | |
| Age, median (IQ) | 66 (53-73) | 63 (52-72) | 67 (54-73) | 0.31 |
| Female sex, n (% ) | 48 (35) | 19 (37) | 29 (34) | 0.68 |
| Prior stroke, n (% ) | 20 (15) | 10 (20) | 10 (12) | 0.18 |

Chi-squared test was used to compare categorical variables, and t-test or Mann-Whitney U test for continuous variables.
* The analysis of permeability ratio, recanalization, and reperfusion is a sub-analysis on 101, 79, and 73 cases respectively.
† All $p<0.05$.
ACA, anterior cerebral artery; IQ, interquartile range; IV-rtPA, intra-venous recombinant tissue Plasminogen Activator; NIHSS, National Institutes of Health Stroke Scale.

| Table 1. Clinical and imaging characteristics. | | | | |
|---|---|---|---|---|
| Atrial fibrillation, n (%) | 16 (12) | 8 (16) | 8 (9) | 0.27 |
| NIHSS, median (IQ) | 15 (12-19) | 18 (13-21) | 14 (11-18) | 0.01 † |
| IV-rtPA, n (%) | 94 (69) | 32 (63) | 62 (72) | 0.25 |
| Intra-arterial treatment, n (%) | 29 (21) | 11 (22) | 18 (21) | 0.93 |
| **Imaging parameters** | | | | |
| Time to admission scan, minutes, median (IQ) | 100 (64-152) | 106 (70-240) | 91 (63-135) | 0.11 |
| **Non-contrast CT** | | | | |
| Early CT signs of infarction, ASPECTS, median (IQ) | 8 (6-10) | 7 (4-9) | 9 (7-10) | 0.0001 † |
| **CT perfusion** | | | | |
| CBV deficit, ASPECTS, mean, (SD) | 4.30 (2.57) | 3.31 (2.32) | 4.89 (2.54) | 0.001 † |
| MTT deficit, ASPECTS, median (IQ) | 1 (0-3) | 1 (0-3) | 2 (0-3) | 0.11 |
| CBV deficit in lentiform nucleus, n (%) | 72 (53) | 32 (63) | 40 (47) | 0.15 |
| CBV deficit in caudate nucleus or ACA territory, n (%) | 54 (39) | 28 (55) | 26 (30) | 0.004 † |
| Permeability ratio, median (IQ) * | 1.36 (1.13-1.88) | 1.66 (1.24-2.60) | 1.30 (1.09-1.54) | 0.002 † |
| **CT angiography** | | | | |
| Clot burden score ≤6, n (%) | 99 (73) | 44 (86) | 55 (65) | 0.006 † |
| Thrombus location ICA/M1 proximal, n (%) | 63 (48) | 33 (67) | 30 (36) | 0.001 † |
| Poor collateral score, n (%) | 62 (46) | 34 (68) | 28 (33) | 0.0001 † |
| **Follow-up CT perfusion & CT angiography** | | | | |
| No recanalization * | 26 (33) | 6 (32) | 20 (33) | 0.89 |
| No reperfusion * | 45 (62) | 16 (76) | 29 (56) | 0.10 |

Chi-squared test was used to compare categorical variables, and t-test or Mann-Whitney U test for continuous variables.
* The analysis of permeability ratio, recanalization, and reperfusion is a sub-analysis on 101, 79, and 73 cases respectively.
† All $p<0.05$.
ACA, anterior cerebral artery; IQ, interquartile range; IV-rtPA, intra-venous recombinant tissue Plasminogen Activator; NIHSS, National Institutes of Health Stroke Scale.

**Table 2. Univariate and multivariate regression.**

| | OR (95% CI) | aOR (95% CI) |
|---|---|---|
| **Clinical parameters** | | |
| Age (per year) | 0.99 (0.96-1.01) | N/A |
| Female sex | 1.17 (0.57-2.40) | 0.88 (0.41-1.90) |
| Prior stroke | 1.90 (0.73-4.95) | 2.08 (0.74-5.91) |
| Atrial fibrillation | 1.79 (0.63-5.11) | 2.74 (0.86-8.70) |
| NIHSS (per point) | 1.12 (1.04-1.21) † | N/A |
| IV-rtPA | 0.65 (0.31-1.36) | 0.56 (0.25-1.22) |
| Intra-arterial treatment | 1.04 (0.45-2.42) | 1.03 (0.42-2.49) |
| **Imaging parameters** | | |
| Time to admission scan (per minute) | 1.002 (0.997-1.007) | 1.003 (0.999-1.006) |
| **Non-contrast CT** | | |
| Early CT signs of infarction, ASPECTS (0-10) | 1.32 (1.14-1.53) † | 1.32 (1.13-1.55) † |
| **CT perfusion** | | |
| CBV deficit, ASPECTS (0-10) | 1.30 (1.12-1.52) † | 1.26 (1.07-1.49) † |
| MTT deficit, ASPECTS (0-10) | 1.20 (0.98-1.46) | 1.14 (0.93-1.41) |
| CBV deficit in lentiform nucleus | 1.90 (0.93-3.85) | 1.53 (0.72-3.22) |
| CBV deficit in caudate nucleus or ACA territory | 2.81 (1.37-5.76) † | 2.01 (0.93-4.32) |
| Permeability ratio * | 2.08 (1.21-3.60) † | 2.35 (1.30-4.24) † |
| **CT angiography** | | |
| Clot burden score ≤6 | 3.43 (1.38-8.55) † | 2.88 (1.11-7.45) † |
| Thrombus location ICA/M1 proximal versus M1 distal, M2 or >M2 | 3.64 (1.73-7.69) † | 3.40 (1.57-7.37) † |
| Poor collateral score | 4.33 (2.05-9.13) † | 3.93 (1.78-8.69) † |
| **Follow-up CT perfusion & CT angiography** | | |
| No recanalization * | 0.92 (0.31-2.79) | 0.92 (0.30-2.81) |
| No reperfusion * | 2.54 (0.81-7.96) | 2.18 (0.67-7.07) |

Legend: see Table 1.
aOR, adjusted odds ratio (for age and NIHSS).

of the patient or impaired renal function. Admission NIHSS and 3 months mRS were not significantly different between patients with or without follow-up imaging.

Of the 137 patients with large MCA on follow-up, 51 (37%) patients developed prominent space-occupying edema. Their baseline clinical and imaging characteristics are shown in Table 1. Median onset time to imaging was 100 minutes and the majority of patients (88%) were imaged within 4.5 hours, and only 6% within the 6-9 hour range. The median time to follow-up was 3.0 days (IQ 2.0-4.0) and not statistically different between patients with and without prominent space-occupying edema. Permeability estimates were only available in 101 patients, and recanalization and reperfusion data in 79 and 73 patients, respectively.

Patients who developed prominent space-occupying edema had a higher NIHSS on admission. In addition, early CT signs of infarction (lower ASPECTS), larger CBV deficit (lower ASPECTS), decreased CBV in caudate nucleus or ACA territory, higher permeability estimates, ICA/proximal M1 occlusions, higher clot burden, and worse collateral scores were more often found in patients with prominent space-occupying edema (all $p<0.05$). Time to admission, percentage of patients treated with IV-rtPA or intra-arterial treatment, recanalization, and reperfusion were not significantly different between patients with large infarcts and prominent space-occupying edema and those without prominent space-occupying edema (Table 1). The OR's of univariate regression are summarized in Table 2.

After adjustment for age and NIHSS, the aOR (Table 2) for prominent space-occupying edema remained significantly higher with more early CT signs of infarction, larger CBV deficit size, higher permeability estimates, more proximal thrombus location, higher clot burden, and poor collateral scores.

7

# Discussion

The main finding of this study is that in patients with a large MCA infarct on follow-up, CT signs of infarction on admission NCCT, larger CBV deficits and higher permeability estimates on admission CTP, proximal thrombus location, a higher clot burden, and worse collateral scores on admission CTA, are significantly associated with the development of prominent space-occupying edema. This suggests that patients that develop prominent space-occupying edema already have an extensive proximal clot and poor collaterals on admission.

Space-occupying edema develops as a combination of swelling of ischemic brain cells (cytotoxic edema) and leakage of fluid through the BBB (vasogenic edema).[28] It is known that the balance between this edema formation and the brain regulatory systems (cerebrovascular autoregulation), that normally maintain cerebral perfusion pressure, is impaired in patients with prominent space-occupying edema.[29] This imbalance possibly occurs because of early involvement of a large ischemic area.

This is supported by the more extensive early CT signs of infarction and larger CBV deficit on admission in patients with prominent space-occupying edema, while the time to scan was not significantly different from patients without prominent space-occupying edema. We suggest that the early development of a large ischemic area in patients with prominent space-occupying edema is a consequence of an extensive proximal clot in combination with poor leptomeningeal collateral status, thereby causing a larger ischemic deficit and increased permeability.

The large MCA infarcts on follow-up in patients without prominent space-occupying edema are presumably the result of a more gradual occurring process. The initial thrombus in those patients is located more distally and this thrombus may extend more proximally over time. As a consequence, areas that still maintained sufficient cerebral perfusion on admission could become infarcted on day 3 NCCT. There was no significant association between treatment with IV-rtPA on admission and recanalization or reperfusion status at day 3 (although recanalization and reperfusion data were only available in 55-74% of patients). This also suggests that the early large extent of the MCA infarct and not recanalization or reperfusion is of importance for the development of prominent space-occupying edema.[30] Moreover, thrombolytic treatment cannot influence the early cascade of events leading to prominent space-occupying edema.

Permeability estimates were a significant factor in univariate regression, and also after adjusting for age and admission NIHSS. This is in agreement with a retrospective study of 120 patients (with 12 patients treated with a hemicraniectomy for prominent space-occupying edema), that showed an association between increased infarct permeability surface area and prominent space-occupying edema occurrence.[9] A relation between duration of ischemia and extent of damage to the BBB has also been shown previously.[31, 32] The time between symptom onset and scan series was shorter in our data (100 minutes versus 310 minutes). This suggests that the BBB damage already occurs early in patients that develop prominent space-occupying edema.

The cause of prominent space-occupying edema in patients with large MCA infarction has not been clarified so far. A study of 818 patients with 208 large MCA infarcts showed that atrial fibrillation was more frequent in large MCA infarcts. They suggested that a cardiac embolus, in contrast to atherosclerotic thrombi from carotid stenosis, occludes a cerebral artery abruptly, leaving little time for collateral pathways to develop.[3] Although our findings support the suggestion that collaterals are insufficiently present in patients that develop prominent space-occupying edema, we did not find a significant difference in history of atrial fibrillation. There is still much controversy about the role of collaterals in both chronic and acute occlusive disease, and the question if cerebral collaterals can develop over time. Our study cannot provide answers for this discussion.

Jaramillo et al. showed in a post mortem analysis of 45 patients that anterior cerebral artery

territory infarcts were associated with prominent space-occupying edema.[12] Moreover, another study stated that ACA involvement contributes to mortality as a mediator of collateral circulation.[19] Our results did not show a significant relation between additional ACA vascular territory, with or without caudate nucleus involvement, and prominent space-occupying edema. A major difference between our study and the study of Jaramillo is that their assessment was done post mortem, after a median of 18 days, while we assessed admission CT scan performed within 9 hours of symptom onset.[12] It is known that the ACA can infarct at a later time-point, secondary to ACA compression caused by subfalcine herniation.[33] This suggests that the ACA involvement in their study was a consequence, rather than a cause, of space-occupying edema formation.

Although age did not make a significant difference in development of prominent space-occupying edema, generalized atrophy in older patients (as demonstrated in Figure 2A) could protect against the occurrence of significant mass effect. However, we did not collect this data to be able to investigate this as a variable.

Strengths of this study are the prospective collection of a large number of patients with prominent space-occupying edema, and the combined use of the information of clinical data with NCCT, CTA, and CTP data. This study also has some limitations.

First, our definition of prominent space-occupying edema was based on follow-up NCCT only. In other papers clinical deterioration was quantified and also considered in the definition of prominent space-occupying edema or malignant MCA infarction.[12, 14, 30] It is however unlikely that patients with prominent space-occupying edema or significant hemorrhage were missed since additional CT scans were always made in case of clinical deterioration during the hospital stay.



Second, the exact time of recanalization is unclear as the follow-up scans were done after 3 days (+/- 2 days), because we had to compromise between short and long term follow-up, to reduce potential radiation risks associated with multiple scans. This potential bias makes it necessary to interpret the results of our recanalization, reperfusion and permeability data with caution.

Third, nine patients had to be excluded because of poor quality CTP at admission, The reason for this was divided between technical (n=4) and patient movement (n=5). The 3 month modified Rankin Sore between these 9 excluded patients and the 137 included patients was not significantly different, so it is unlikely that this caused any bias.

Fourth, patients with early spontaneous recanalization could potentially have influenced our results, since CTP and CTA parameters may not always be accurate. However, in these patients the ischemic changes on NCCT should still be indicative of the severity of the ischemia and thereby associated with prominent mass effect.

# Conclusions

In patients with large MCA infarctions on follow-up, early CT signs of infarction on admission NCCT, larger CBV deficits and higher permeability estimates on admission CTP, and more proximal thrombus location, higher clot burden, and worse collateral scores on admission CTA, are significantly associated with prominent space-occupying edema. This suggests that the prominent space-occupying edema in these patients develops due to a combination of extensive proximal occlusion and poor collaterals, which rapidly leads to a large area of ischemia with increased permeability.

# References


1. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53:309-315
2. Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. Intensive Care Med. 1998;24:620-623
3. Heinsius T, Bogousslavsky J, Van Melle G. Large infarcts in the middle cerebral artery territory. Etiology and outcome patterns. Neurology. 1998;50:341-350
4. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurology. 2007;6:215-222
5. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurology. 2009;8:326-333
6. Arch AE, Sheth KN. Malignant cerebral edema after large anterior circulation infarction: a review. Curr Treat Options Cardiovasc Med. 2014;16:275
7. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. Cerebrovasc Dis. 2008;25:176-184
8. Rudolf J, Grond M, Stenzel C, Neveling M, Heiss WD. Incidence of space-occupying brain edema following systemic thrombolysis of acute supratentorial ischemia. Cerebrovasc Dis. 1998;8:166-171
9. Bektas H, Wu TC, Kasam M, Harun N, Sitton CW, Grotta JC, Savitz SI. Increased blood-brain barrier permeability on perfusion CT might predict malignant middle cerebral artery infarction. Stroke. 2010;41:2539-2544
10. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751
11. Sykora M, Steiner T, Rocco A, Turcani P, Hacke W, Diedler J. Baroreflex sensitivity to predict malignant middle cerebral artery infarction. Stroke. 2012;43:714-719
12. Jaramillo A, Gongora-Rivera F, Labreuche J, Hauw JJ, Amarenco P. Predictors for malignant middle cerebral artery infarctions: a postmortem analysis. Neurology. 2006;66:815-820
13. Wartenberg KE. Malignant middle cerebral artery infarction. Curr Opin Crit Care. 2012;18:152-163

14. Minnerup J, Wersching H, Ringelstein EB, Heindel W, Niederstadt T, Schilling M, Schabitz WR, Kemmling A. Prediction of malignant middle cerebral artery infarction using computed tomography-based intracranial volume reserve measurements. Stroke. 2011;42:3403-3409

15. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37

16. 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. Lancet. 2000;355:1670-1674

17. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025

18. Dohmen C, Galldiks N, Bosche B, Kracht L, Graf R. The severity of ischemia determines and predicts malignant brain edema in patients with large middle cerebral artery infarction. Cerebrovasc Dis. 2012;33:1-7

19. Walcott BP, Miller JC, Kwon CS, Sheth SA, Hiller M, Cronin CA, Schwamm LH, Simard JM, Kahle KT, Kimberly WT, Sheth KN. Outcomes in Severe Middle Cerebral Artery Ischemic Stroke. Neurocrit Care. 2014;21:20-26

20. van Seeters T, Biessels GJ, Niesten JM, van der Schaaf IC, Dankbaar JW, Horsch AD, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Reliability of Visual Assessment of Non-Contrast CT, CT Angiography Source Images and CT Perfusion in Patients with Suspected Ischemic Stroke. PLoS One. 2013;8:e75615

21. Kasner SE, Demchuk AM, Berrouschot J, Schmutzhard E, Harms L, Verro P, Chalela JA, Abbur R, McGrade H, Christou I, Krieger DW. Predictors of fatal brain edema in massive hemispheric ischemic stroke. Stroke. 2001;32:2117-2123

22. Soares BP, Tong E, Hom J, Cheng SC, Bredno J, Boussel L, Smith WS, Wintermark M. Reperfusion is a more accurate predictor of follow-up infarct volume than recanalization: a proof of concept using CT in acute ischemic stroke patients. Stroke. 2010;41:e34-40

23. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, O'Reilly C, Hudon ME, Hu WY, Coutts SB, Barber PA, Watson T, Roy J, Demchuk AM. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3:230-236

24. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. AJNR Am J Neuroradiol. 2009;30:525-531

25. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61:533-543

26. El-Mitwalli A, Saad M, Christou I, Malkoff M, Alexandrov AV. Clinical and sonographic patterns of tandem internal carotid artery/middle cerebral artery occlusion in tissue plasminogen activator-treated patients. Stroke. 2002;33:99-102

27. Tomsick T, Broderick J, Carrozella J, Khatri P, Hill M, Palesch Y, Khoury J. Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol. 2008;29:582-587

28. Heo JH, Han SW, Lee SK. Free radicals as triggers of brain edema formation after stroke. Free Radic Biol Med. 2005;39:51-70

29. Dohmen C, Bosche B, Graf R, Reithmeier T, Ernestus RI, Brinker G, Sobesky J, Heiss WD. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. Stroke. 2007;38:56-61

30. Thomalla G, Hartmann F, Juettler E, Singer OC, Lehnhardt FG, Kohrmann M, Kersten JF, Krutzelmann A, Humpich MC, Sobesky J, Gerloff C, Villringer A, Fiehler J, Neumann-Haefelin T, Schellinger PD, Rother J. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: A prospective multicenter observational study. Ann Neurol. 2010;68:435-445

31. Ito U, Go KG, Walker JT, Jr., Spatz M, Klatzo I. Experimental cerebral ischemia in Mongolian gerbils III. Behaviour of the blood-brain barrier. Acta Neuropathol. 1976;34:1-6

32. Todd NV, Picozzi P, Crockard A, Russell RW. Duration of ischemia influences the development and resolution of ischemic brain edema. Stroke. 1986;17:466-471

33. Grossman RI, Yousem DM. Neuroradiology, the requisites. 2d Ed. Philidelphia, Pennsylvania, Mosby, Elsevier Inc. 2003:261-263

# CHAPTER 8

# Blood-brain barrier permeability measurements with CT-perfusion predict prominent edema in acute ischemic stroke.

Alexander D. Horsch, Birgitta K. Velthuis, Edwin Bennink, Hugo W.A.M. de Jong, Tom van Seeters, Tom A. Stemerdink, H. Bart van der Worp, L. Jaap Kappelle, Jeannette Hofmeijer, Yolanda van der Graaf, Willem P.Th.M. Mali, Jan Willem Dankbaar, on behalf of the DUST investigators

Submitted

# Abstract

## Background

Early prediction of prominent space-occupying cerebral edema may guide treatment decisions in acute ischemic stroke. This study aimed to investigate the association between CT derived blood-brain barrier permeability (BBBP) measurements and prominent edema, and evaluate its additional predictive value.

## Methods

From the Dutch acute stroke study (DUST), patients were selected with a middle cerebral artery occlusion on admission CT angiography, available extended CT perfusion on admission, and follow-up non-contrast CT within 7 days. Prominent edema was defined on follow-up CT as a midline shift ≥5 mm. Patient baseline and treatment characteristics, and CT imaging parameters regarding occlusion site, infarct size and BBBP were collected. The association between BBBP and 2 pre-selected variables (clot burden and poor collaterals), and prominent edema was evaluated using univariate and multivariate logistic regression. The additional diagnostic value of BBBP was evaluated by comparing area under the curves (AUCs) of the receiver operating characteristics (ROC) curves of 2 multivariate models, with and without BBBP.

## Results

From the included 295 patients, 33 (11%) developed prominent edema. In univariate analysis all 3 variables showed a significant association with edema: BBBP (odds ratio (OR) 3.01, 95 CI% 1.94-4.84), clot burden (OR 1.60, 95 CI% 1.37-1.86) and poor collaterals (OR 10.27, 95 CI% 4.51-23.38). The AUC for a model including BBBP (0.88, 95 CI% 0.81-0.94) was significantly (p=0.02) higher than with clot burden and collaterals alone (0.85, 95 CI% 0.77-0.94). A specificity of 82% could be combined with a sensitivity of 83% for the prediction of prominent edema.

## Conclusion

BBBP has additional predictive value for the prediction of prominent edema in acute ischemic stroke patients.

# Introduction

Around 5-10% of patients with a large middle cerebral artery (MCA) infarction show rapid neurological deterioration due to prominent space-occupying cerebral edema.[1] The occurrence of prominent edema after MCA infarction is associated with a mortality of up to 80%, if left untreated. Treatment options are limited and include edema reduction with medical treatment and surgical decompression.[2]

A pooled analysis of 3 randomized controlled trials showed that hemicraniectomy, performed within 48 hours of symptom onset, significantly reduces mortality and improves functional outcome.[3] Some studies suggest that functional outcome is better if surgery is performed before the onset of prominent edema formation and clinical deterioration.[3, 4] Because surgery also carries significant risks, careful and early patient selection is important. Higher admission National Institutes of Health Stroke Scale (NIHSS), female sex, more proximal occlusion site, larger infarct size, basal ganglia involvement and additional vascular territory involvement are known risk factors for space-occupying edema.[5-8]

Cerebral edema is caused by cytotoxic and vasogenic edema, and vasogenic edema occurs when the blood-brain barrier (BBB) is disrupted. Increased BBB permeability (BBBP) has been suggested as a possible predictor of prominent edema.[9] Patients with acute stroke symptoms are increasingly imaged with a dedicated stroke protocol, including non-contrast CT (NCCT) to excluded bleeding, CT angiography (CTA) to identify the location and extent of the arterial occlusion and degree of collateral circulation, and CT perfusion (CTP) to assess location and size of compromised tissue perfusion.[10] Nonlinear regression (NLR) permeability is a method to estimate BBBP using an extended CTP acquisition, that has recently been shown to result in more reliable permeability estimates compared to the estimates obtained with the Patlak method.[11]

The aim of this study is to investigate the use of blood-brain barrier permeability estimates using NLR as a predictor for prominent cerebral edema, and to evaluate its additional predictive value by comparing it to other important imaging variables.



# Materials and methods

## Patient selection

All patients were selected from the prospective multi-center Dutch acute stroke study (DUST) study. The study protocol and main findings have been published previously.[10, 12] In short, this study included adult patients between May 2009 and August 2013 who underwent a NCCT, CTA and CTP within 9 hours after onset of acute ischemic stroke symptoms.[10, 12] This study was approved by the local institutional ethical review boards of the participating centers. All

patients or family gave signed informed consent, unless a patient died before consent could be obtained. In that case, the medical ethics committee waived the need for consent.[10, 12]

For the current study, all patients were included with an occlusion in the internal carotid artery (ICA), MCA M1 or M2 segment on admission CTA, and availability of admission extended CTP, and a follow-up NCCT within 7 days. Exclusion criteria were hemorrhagic transformation with mass effect (European Cooperative Acute Stroke Study (ECASS) classification, parenchymal hemorrhage (PH) type-2) on follow-up NCCT or poor quality (extended) CTP. PH type-2 were excluded because the focal blood-brain barrier disturbance in these patients is necessarily larger to allow erythrocytes to cross and treatment options would be different. The inclusion process is clarified in the flow chart (Figure 1). We collected clinical data on age, sex, history of stroke, admission NIHSS, time from symptoms to scan, and intra-venous recombinant Plasminogen Activator (IV-rtPA) treatment.

## Imaging protocol

On admission brain NCCT and CTP, and CTA of the cerebral and cervical vessel were performed. A follow-up NCCT was planned at day 3 and also performed in case of clinical deterioration (within 7 days), or earlier if patients were discharged. Multi-detector CT scanners were used with the number of detectors ranging from 40 to 320 (Philips, Siemens, Toshiba, GE). NCCT was performed with 120 kV, 300-375 mAs, and slice thickness of 5 mm.

The CTP was performed with 80 kV and 150 mAs, and consisted of successive gantry rotations in cine mode during intra-venous administration of 40 ml non-ionic contrast material followed by 40 ml of saline with a flow of 6 ml/sec. Temporal sampling was obtained every 2 seconds for the first 50 seconds with 6 additional acquisitions every 30 seconds, from 60 seconds up to 210 seconds. CTP coverage included at least the level of the basal ganglia

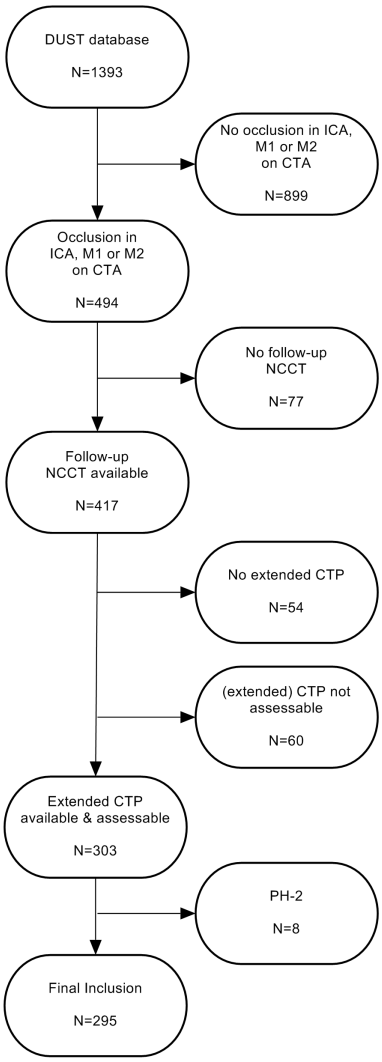



Figure 1. Inclusion flow chart.

to the lateral ventricles to be able to assess both Alberta Stroke Program Early CT Score (ASPECTS) levels.[13]

A CTA was acquired from aortic arch to the cranial vertex with 50-70 ml contrast followed by 40 ml of saline, both with a flow of 6 ml/s. The scan delay after intra-venous injection was calculated from time to peak arterial enhancement on CTP, or by trigger-based Hounsfield threshold measurement of contrast enhancement in the aortic arch.

## Image analysis

NCCT: On admission scans we evaluated the presence of dense vessel sign and early CT signs using ASPECTS.[13] On follow-up imaging the presence of prominent edema was defined as a midline shift ≥5 mm, as previously used in literature.[5, 6, 14, 15] Additionally, any hemorrhagic transformation was noted and classified according to the ECASS criteria.[16] This was done to identify patients with a parenchymal hemorrhage type-2, as the midline shift in those patients is considered to be secondary to the large hemorrhage.[16]

CTP: Cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP) were automatically calculated from CTP data utilizing commercially available CTP software (Extended Brilliance Workstation 4.5, Philips Healthcare). The non-occluded internal carotid artery (ICA) or anterior cerebral artery (ACA) was chosen as arterial input function.[17] The superior sagittal sinus was used as venous output function. Presence of a perfusion deficit on admission was defined as a focal asymmetry on the MTT, CBF or CBV map matching a part or the whole of the MCA flow territory. The infarct core was evaluated on CBV maps and classified with ASPECTS.[18]

Permeability values were calculated from the extended CTP acquisition with custom-made software.[11] This software applies a nonlinear method that describes an impulse response function obtained from a mathematical response model to estimate the permeability surface area.[11] In this study, nonlinear permeability was measured as a hemisphere ratio of the total affected hemisphere divided by the total unaffected hemisphere.[11]

CTA: Admission CTA provided data on intra-cranial thrombus location, clot burden score (CBS), and collateral score.[19-21] Thrombus location was classified to the most proximal site of occlusion unless there was a combined extra-cranial internal carotid (ICA) occlusion with a more distal MCA occlusion with an open ICA top (tandem lesion), which was classified at the level of the MCA occlusion (proximal flow maintained by Circle of Willis collaterals).[22] CBS was obtained as previously described.[19] The collateral score was evaluated by visual assessment of the MIP images and categorized as poor or good (cutoff 50%) compared to the non-symptomatic hemisphere.

All imaging data were evaluated by one of three observers, all with at least 5 years of experience in stroke imaging.[10] Only the side of symptoms was provided for the evaluation.

**Table 1. Patient characteristics.**

| | All patients N=295 | Prominent edema N=33 | No prominent edema N=262 | P-value |
|---|---|---|---|---|
| **Clinical parameters** | | | | |
| Age, median (IQ) | 68 (57-77) | 63 (50-71) | 68 (58-77) | 0.03* |
| Female sex, n (% ) | 129 (44) | 10 (30) | 119 (45) | 0.10 |
| Prior stroke, n (% ) | 56 (19) | 7 (22) | 49 (19) | 0.67 |
| NIHSS, median (IQ) | 12 (6-17) | 17 (13-21) | 11 (6-16) | <0.0001* |
| **Treatment** | | | | |
| IV-rtPA, n (%) | 205 (70) | 19 (58) | 186 (71) | 0.12 |
| **Imaging parameters** | | | | |
| Time from symptoms to scan, minutes, median (IQ) | 104 (64-158) | 135 (75-249) | 102 (63-143) | 0.046* |
| **Admission non-contrast CT** | | | | |
| Early CT signs, ASPECTS 0-10, median (IQ) | 10 (8-10) | 7 (4-9) | 10 (9-10) | <0.0001* |
| **Admission CT perfusion** | | | | |
| Size infarct core, ASPECTS 0-10, median (IQ) | 7 (4-9) | 3 (1-4) | 7 (5-9) | <0.0001* |
| NLR permeability, (BBBP) median (IQ) | 1.22 (1.05-1.49) | 1.67 (1.28-2.63) | 1.19 (1.03-1.42) | <0.0001* |
| **Admission CT angiography** | | | | |
| Clot burden score, 0-10, median (IQ) | 7 (6-9) | 4 (1-6) | 8 (6-9) | <0.0001* |
| Thrombus location ICA/M1 proximal, n (%) | 66 (22) | 22 (67) | 44 (17) | <0.0001* |
| Poor collateral score, n (%) | 78 (26) | 24 (73) | 54 (21) | <0.0001* |

Chi-squared test was used to compare categorical variables and Mann–Whitney U test for continuous variables.
* All p< 0.05
ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; BBBP, blood-brain barrier permeability; CBV, cerebral blood volume; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; ICA, internal carotid artery; IQ, interquartile range; IV-rtPA, intra-venous recombinant tissue Plasminogen Activator; NIHSS, National Institutes of Health Stroke Scale; NCCT, non-contrast CT; NLR, nonlinear regression.

## Statistical analysis

Presence of prominent edema on follow-up NCCT was used as outcome measure, as previously used.[5, 6, 14, 15] Clinical data considered were age, sex, history of stroke, admission NIHSS, time from symptoms to scan and rtPA treatment and the imaging variables were dense vessel sign (yes/no) and early CT signs (ASPECTS 0-10) on NCCT; infarct core size (ASPECTS 0-10), and nonlinear permeability ratio on CTP; and thrombus location (ICA/proximal M1 versus a distal M1, M2 or >M2), CBS (0-10), and collateral score (good/poor) on CTA.[20] Data were presented as number and percentage, means with SD, or as medians with inter-quartile range. Differences in clinical and imaging data were calculated with the chi-squared test to compare categorical variables and the Mann–Whitney U test for continuous variables.

The association between BBBP and 2 other potential predictor variables, and prominent edema was analyzed using univariate and multivariate logistic regression. As we only had a limited number of outcomes, a maximum of 2 additional variables could be evaluated (to have at least 10 outcomes per variable). CTA derived CBS and collateral score were pre-selected as variables because a CTA is done in most centers as a standard work-up for intra-arterial stroke treatment, and CBS and collateral score are associated with development of edema.[15, 20, 23, 24] For each variable the odds ratio (OR) and 95% confidence interval (CI) was calculated. Two multivariate models were created: one with all 3 variables including BBBP, and the second without BBBP. Receiver operating characteristics (ROC) curves were created by calculating the predicted probabilities of the 3 variables separately, and of the two multivariate models. The additional predictive value of BBBP was assessed by comparing the area under the curve (AUC) of the two ROC using the DeLong test (one-sided).[25] From both curves sensitivity and specificity were determined for 3 cutoff values: high specificity, high sensitivity and the optimum combination of both. Significance was pre-defined at $p<0.05$. Statistical computations were carried out using SPSS 23.0 (IBM corporation, NY, USA).

# Results

Of the 1393 patients included in the DUST study, 494 had an occlusion in the ICA, MCA M1 or M2 segment. Of those, 77 did not have follow-up NCCT (e.g. due to good clinical condition), another 54 had no extended CTP, and in 60 cases the (extended) CTP was not assessable due to technical reasons. Eight patients were excluded because of PH-2 on follow-up. Age, mRS at 3 months and admission NIHSS were not significantly different between excluded and included patients. Finally, 295 patients were included, of whom 33 developed prominent edema (11%, Figure 1).

Clinical and imaging characteristics of patients with and without prominent edema on follow-up are summarized in Table 1. Patients with prominent edema were younger, had a higher

**Table 2. Univariate and multivariate analysis for BBBP and other pre-selected predictors of prominent edema.**

| | Univariate | | Multivariate clot burden score and collateral score | | Multivariate BBBP, clot burden score and collateral score | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| NLR permeability (BBBP) | 3.01 | 1.94-4.84 | N/A | N/A | 1.84 | 1.07-3.18 |
| Clot burden score (0-10) | 1.60 | 1.37-1.86 | 1.48 | 1.26-1.75 | 1.42 | 1.20-1.68 |
| Collateral score | 10.27 | 4.51-23.38 | 6.07 | 2.52-14.64 | 5.29 | 2.16-12.98 |

BBBP, blood-brain barrier permeability.

**Table 3. AUC of BBBP, clot burden score and collateral score separately, and of the combination of clot burden score and collateral score, with or without BBBP.**

| | AUC | 95% CI |
|---|---|---|
| BBBP | 0.77 | 0.68-0.86 |
| Clot Burden Score | 0.80 | 0.70-0.89 |
| Collateral Score | 0.76 | 0.67-0.86 |
| Clot burden score and collateral score | 0.85 | 0.77-0.94 |
| BBBP, clot burden score and collateral score | 0.88 | 0.81-0.94 |

AUC, area under the curve; BBBP, blood-brain barrier permeability.

NIHSS on admission, and a longer time from symptom onset to admission CT scans. All imaging parameters collected were significantly different between patients with and without edema.

BBBP, CBS and collateral score all showed positive ORs for prominent edema in univariate and multivariate analysis (Table 2). The univariate ROC curves and the ROC curves of the 2 models are presented in Figure 2. The AUC of the model with infarct core size, clot burden and BBBP (AUC 0.88, 95%CI 0.81-0.94) was significantly higher (p=0.02) than the model without BBBP (AUC 0.85, 95%CI 0.77-0.94) (Table 3).

With the model combining BBBP, clot burden and collateral score, a high sensitivity of 91% combined with a specificity of 65%, a high specificity of 93% with a sensitivity of 52% or an 'optimum' combination of 82% specificity with a sensitivity of 83% can be selected (Table 4). With this 'optimum' combination, 6 of 33 patients with proven prominent edema would not have been identified (false negatives) and 45 of 72 patients with a positive test would have been incorrectly identified as prominent edema patients (false positives). This gives a positive predictive value (PPV) of 38% and a negative predictive value (NPV) of 97%, with 217 (74%) patients correctly identified as not being at risk for prominent edema.

**Table 4. Sensitivity, specificity, PPV and NPV for the combination of BBBP, clot burden score and collateral score.**

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| High sensitivity | 91 | 65 | 25 | 98 |
| High specificity | 52 | 93 | 49 | 94 |
| Optimum | 82 | 83 | 38 | 97 |

BBBP, blood-brain barrier permeability; PPV, positive predictive value; NPV, negative predictive value.

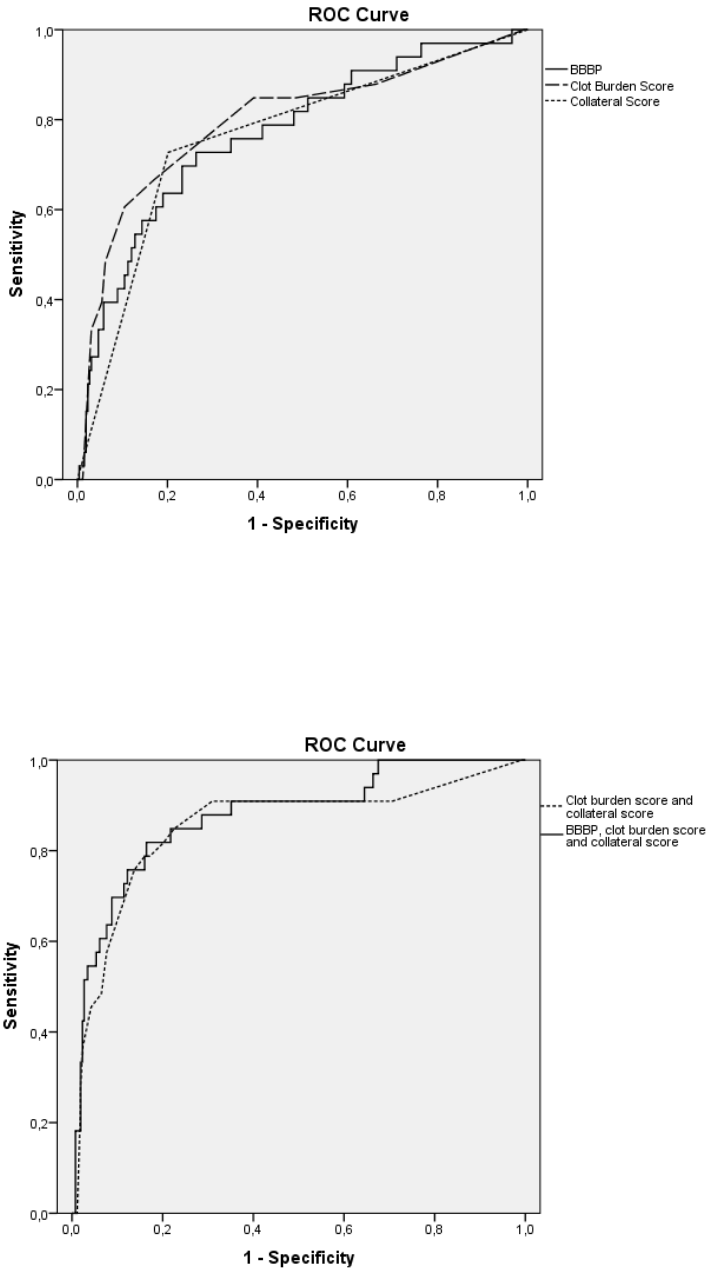



Figure 2: ROC curves.

# Discussion

The most important finding in this study is that permeability estimated with nonlinear regression obtained on admission is an early predictor of prominent edema and significantly improves prediction compared to the combination of clot burden and collateral score. This combination of CT imaging parameters can predict prominent edema with good sensitivity and specificity. The finding that increased permeability is related to prominent edema suggest that vasogenic edema plays a more important role than previously thought.

We were able to find cut-off values for the multivariate model with a high specificity while maintaining a good sensitivity. This is important in decision making because early treatment could improve outcome. Further improvement is expected if this treatment can be applied before the irreversible cascade of edema formation starts and extensive brain damage occurs. However, treatment with hemicraniectomy is an extensive and potentially high risk procedure, and only patients that are certain to develop prominent edema should be selected. This means that the predictive test should ideally have a very high specificity.

With our test results acute ischemic stroke patients can be divided into 3 groups: patients that will develop prominent edema with certainty, patients that with certainty will not develop prominent edema and those patients that cannot be included in either of these two groups. In our population 74% (97% NPV) of patients could be confidently included in the group not at risk of developing space-occupying edema. Consequently, these patients will not require extensive monitoring to identify space-occupying edema. With our 83% specificity, 45 patients (62%, 1-PPV) with a positive test would receive a hemicraniectomy unnecessarily. This implies that for these patients the peri-operative risk of hemicraniectomy needs to be weighed against its benefits in preventing prominent edema. For obvious ethical reasons, the peri-operative risks of hemicraniectomy in patients not at risk of proceeding to prominent edema is unknown. Alternatively, these high-risk patients could be monitored more frequently by clinical assessment, microdialysis or additional imaging for early signs of clinical deterioration and to avoid unnecessary risks of hemicraniectomy.[26] The usefulness of the combination of BBBP, clot burden and collateral score to predict prominent edema has to be verified in a RCT, with treatment decisions based on these parameters.

Only one other study investigated the predictive value of BBBP for edema and this retrospective study of 122 patients from a registry of MCA infarcts with 12 outcomes, showed a positive OR up to 1.9, depending on the size of the infarct permeability area.[9] Major differences with our study are their use of the modified Patlak model, a much shorter acquisition time of 75 seconds and a lower number of outcomes. In our larger study we used a nonlinear model to estimate permeability, and we compared and combined these estimates with other frequently used CT angiography parameters. Our PPV was much higher (38% compared to 10%), while our NPV was comparable (97% compared to 100%). These differences make

our study a valuable addition to their findings. Other papers with >10 outcomes investigating the relation between permeability and prominent edema could not be found, but it is possible that negative results failed to be published.

In other studies with CT or MRI within 8 hours after symptom onset, sensitivity for predicting prominent edema ranged from 52% to 100% and specificity from 72% to 100%.[7, 9, 14, 27-29] Only one study, with 17 patients and 9 outcomes, reported specificity and sensitivity values of 100% for predicting prominent edema.[14] This study compared relative reduction in CBF to the contra-lateral hemisphere with PET within 24 hrs, which makes these results less useful as PET is usually not available 24/7 and prediction should preferably be available at an early time point.[14] A specificity higher than 95% was found for diffusion weighted imaging (DWI) volume > 78ml or > 82ml and CBV lesion volume/CSF volume ratio >0.92 (all with specificities also higher than 95%).[7, 27, 28] The use of DWI is less practical as MRI is also often not available 24/7 and monitoring equipment is often MRI-incompatible. The CBV lesion volume/cerebrospinal fluid (CSF) volume ratio also showed a high sensitivity and specificity for prominent edema but this predictor was derived from a retrospective study with a highly selected population of 64 patients, with 50% developing prominent edema.[28] This raises concerns about the reproducibility of these results in other stroke populations. Another more recent study also investigated a highly selected patient group, with 31% developing malignant edema, identifying collateral score <2 (≤ 50% MCA territory compared to collateral hemisphere) as an independent predictor but without providing sensitivity or specificity data.[24]

Major strengths of this study are that data are prospectively collected, with a combination of clinical and imaging data, and that it reproduces the associations with prominent edema found in other studies.[5-8]

There are also limitations. First, we had to exclude 27% of patients because extended CTP on admission or follow-up NCCT was missing. Age, modified Rankin Score at 3 months and admission NIHSS were not significantly different between excluded and included patients. Moreover, because patients received additional follow-up NCCT in case of clinical deterioration it is unlikely that patients with prominent edema were missed.

Second, only 33 outcomes were available which prevented us from including more variables such as patient characteristics in the multivariate analysis. Comparable numbers of outcomes are found in the largest recent CT and MRI studies.[7, 27, 28] The occurrence of prominent edema is relatively low and its incidence might recently have been reduced due to the improved stroke awareness and therefore shorter time to treatment.

# Conclusions

Blood-brain barrier permeability estimation with CTP is an early predictor of prominent edema and improves prediction compared to CTA clot burden and collateral score variables. This combination of 3 imaging variables can predict prominent edema with good sensitivity and specificity, and could possibly be used to identify patients who require intensive monitoring and could benefit from preventive decompressive craniectomy.

# References


1. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53:309-315

2. Flint AC, Faigeles BS, Cullen SP, Kamel H, Rao VA, Gupta R, Smith WS, Bath PM, Donnan GA. THRIVE Score Predicts Ischemic Stroke Outcomes and Thrombolytic Hemorrhage Risk in VISTA. Stroke. 2013;44:3365-3369

3. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurology. 2007;6:215-222

4. Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. Early hemicraniectomy in patients with complete middle cerebral artery infarction. Stroke. 1998;29:1888-1893

5. Sykora M, Steiner T, Rocco A, Turcani P, Hacke W, Diedler J. Baroreflex sensitivity to predict malignant middle cerebral artery infarction. Stroke. 2012;43:714-719

6. Walcott BP, Miller JC, Kwon CS, Sheth SA, Hiller M, Cronin CA, Schwamm LH, Simard JM, Kahle KT, Kimberly WT, Sheth KN. Outcomes in Severe Middle Cerebral Artery Ischemic Stroke. Neurocrit Care. 2014;21:20-26

7. Thomalla G, Hartmann F, Juettler E, Singer OC, Lehnhardt FG, Kohrmann M, Kersten JF, Krutzelmann A, Humpich MC, Sobesky J, Gerloff C, Villringer A, Fiehler J, Neumann-Haefelin T, Schellinger PD, Rother J. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: A prospective multicenter observational study. Ann Neurol. 2010;68:435-445

8. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. Cerebrovasc Dis. 2008;25:176-184

9. Bektas H, Wu TC, Kasam M, Harun N, Sitton CW, Grotta JC, Savitz SI. Increased blood-brain barrier permeability on perfusion CT might predict malignant middle cerebral artery infarction. Stroke. 2010;41:2539-2544

10. van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Niesten JM, Luitse MJ, Majoie CB, Vos JA, Schonewille WJ, van Walderveen MA, Wermer MJ, Duijm LE, Keizer K, Bot JC, Visser MC, van der Lugt A, Dippel DW, Kesselring FO, Hofmeijer J, Lycklama ANGJ, Boiten J, van Rooij WJ, de Kort PL, Roos YB, van Dijk EJ, Pleiter CC, Mali WP, van der Graaf Y, Velthuis BK. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. Cerebrovasc Dis. 2015;40:258-269

11. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751

12. van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, Horsch AD, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. BMC Neurol. 2014;14:37

13. 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. Lancet. 2000;355:1670-1674

14. Dohmen C, Galldiks N, Bosche B, Kracht L, Graf R. The severity of ischemia determines and predicts malignant brain edema in patients with large middle cerebral artery infarction. Cerebrovasc Dis. 2012;33:1-7

15. Horsch AD, Dankbaar JW, Stemerdink TA, Bennink E, van Seeters T, Kappelle LJ, Hofmeijer J, de Jong HW, van der Graaf Y, B.K. V. Imaging Findings Associated with Space-Occupying Edema in Patients with Large Middle Cerebral Artery Infarcts. AJNR Am J Neuroradiol. 2016;May;37(5):831-7

16. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017-1025

17. Niesten JM, van der Schaaf IC, Riordan AJ, de Jong HW, Mali WP, Velthuis BK. Optimisation of vascular input and output functions in CT-perfusion imaging using 256(or more)-slice multidetector CT. Eur Radiol. 2013;23:1242-1249

18. van Seeters T, Biessels GJ, Niesten JM, van der Schaaf IC, Dankbaar JW, Horsch AD, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK. Reliability of Visual Assessment of Non-Contrast CT, CT Angiography Source Images and CT Perfusion in Patients with Suspected Ischemic Stroke. PLoS One. 2013;8:e75615

19. Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, O'Reilly C, Hudon ME, Hu WY, Coutts SB, Barber PA, Watson T, Roy J, Demchuk AM. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3:230-236

20. Tan IYL, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. AJNR Am J Neuroradiol. 2009;30:525-531

21. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61:533-543

22. El-Mitwalli A, Saad M, Christou I, Malkoff M, Alexandrov AV. Clinical and sonographic patterns of tandem internal carotid artery/middle cerebral artery occlusion in tissue plasminogen activator-treated patients. Stroke. 2002;33:99-102

23. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11-20

24. Kim H, Jin ST, Kim YW, Kim SR, Park IS, Jo KW. Predictors of malignant brain edema in middle cerebral artery infarction observed on CT angiography. J Clin Neurosci. 2015;22:554-560

25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-845

26. Dohmen C, Bosche B, Graf R, Reithmeier T, Ernestus RI, Brinker G, Sobesky J, Heiss WD. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. Stroke. 2007;38:56-61

27. Kruetzelmann A, Hartmann F, Beck C, Juettler E, Singer OC, Kohrmann M, Kersten JF, Sobesky J, Gerloff C, Villringer A, Fiehler J, Neumann-Haefelin T, Schellinger PD, Rother J, Thomalla G. Combining magnetic resonance imaging within six-hours of symptom onset with clinical follow-up at 24 h improves prediction of 'malignant' middle cerebral artery infarction. Int J Stroke. 2014;9:210-214

28. Minnerup J, Wersching H, Ringelstein EB, Heindel W, Niederstadt T, Schilling M, Schabitz WR, Kemmling A. Prediction of malignant middle cerebral artery infarction using computed tomography-based intracranial volume reserve measurements. Stroke. 2011;42:3403-3409

29. Dittrich R, Kloska SP, Fischer T, Nam E, Ritter MA, Seidensticker P, Heindel W, Nabavi DG, Ringelstein EB. Accuracy of perfusion-CT in predicting malignant middle cerebral artery brain infarction. J Neurol 2008;255:896-902

# CHAPTER 9

## Summary and general discussion
## Samenvatting

# Key findings of this thesis:

## Reperfusion and recanalization[1]

Recanalization and reperfusion are strongly associated but not always equivalent.

Only the total ischemic area on CTP is an independent predictor of complete reperfusion.

Patients with an intra-cranial internal carotid artery occlusion do not show complete reperfusion after intra-venous recombinant tissue Plasminogen Activator treatment.

## Stroke severity, patients characteristics and blood-brain permeability values[2]

Early CT signs of ischemia are related to higher blood-brain barrier permeability values in the infarct core (Patlak model).

## Reperfusion, blood-brain permeability and hemorrhagic transformation[3-5]

Increased risk of hemorrhagic transformation after acute ischemic stroke treatment is not dependent on reperfusion status.

The percentage of hemorrhagic transformation is higher in patients treated with intra-venous recombinant tissue Plasminogen Activator, irrespective of reperfusion status.

Blood-brain barrier permeability values obtained with nonlinear regression have superior discriminative power for predicting hemorrhagic transformation compared with blood-brain barrier permeability values obtained with Patlak analysis.

The blood-brain barrier permeability values (nonlinear regression) are related to the occurrence of hemorrhagic transformation, but do not improve the predictive value when added to the variables age and admission National Institutes of Health Stroke Scale.

## Blood-brain permeability and malignant edema[6, 7]

An extensive proximal occlusion, poor collaterals, and a larger total ischemic deficit with higher blood-brain permeability play a role in the development of malignant edema in large middle cerebral artery infarcts.

Blood-brain permeability values (nonlinear regression) are an early predictor of malignant edema and improve prediction with clot burden score and collateral score.

# Summary and general discussion

Although treatment for acute ischemic stroke patients has improved in the last few years, severe complications like hemorrhagic transformation and malignant edema still occur. Reducing the number and severity of these complications could improve stroke outcome.[8-15] Imaging techniques could be used to monitor the progression of the disease and the result of treatment. Imaging can also be used to predict the occurrence of these complications, although at the present time adequate treatment to prevent these complications is not widely available.[16, 17] More extensive imaging with CT perfusion (CTP) could potentially delay treatment, which is important because of the relation between a shorter time to treatment and better outcome (time is brain).[18] Before imaging techniques can be used in routine clinical practice they have to be shown useful in a research setting. Therefore, thorough evaluation of new imaging techniques is needed before implementation into standard clinical practice can be advised.

In this thesis the relation between two new imaging parameters obtained with CTP (reperfusion and blood-brain barrier permeability) and two of the most devastating complications (hemorrhagic transformation and space-occupying cerebral edema or malignant edema) in acute ischemic stroke was investigated.

# Summary

## Reperfusion and recanalization

The aim of intra-venous thrombolysis or intra-arterial thrombectomy is to achieve timely revascularization by dissolving or removing the occluding thrombus load in the affected territory. Revascularization can be divided into 3 components: recanalization, collateralization and reperfusion.[19] Better understanding of the relation between these components could improve the assessment of results of therapy.

The results of the study in **chapter 2** show that recanalization and reperfusion are strongly associated but not always equivalent.[1] Complete reperfusion can occur without complete recanalization if anastomotic channels or good collaterals are present. Incomplete reperfusion can occur despite complete recanalization due to (1) breakup of the primary clot into fragments leading to distal embolization of smaller vasculature not visible on CT angiography (CTA), (2) incomplete microcirculatory reperfusion or (3) persistent thrombus in the small capillaries.[20-23] This suggests that it might be beneficial to assess both recanalization and reperfusion in the evaluation of intra-venous thrombolysis. This needs to be considered in connection with the time to treatment, because futile recanalization and reperfusion can occur if the ischemic time is too long and the neurons have already died.

The main predictors of complete reperfusion were lower National Institutes of Health Stroke Scale (NIHSS) on admission, lower clot burden, more distal thrombus location, and good collateral score on CTA, and smaller infarct core and total ischemic area on CTP. In multivariate analysis only total ischemic area on CTP was an independent predictor of complete reperfusion. This is not surprising as a smaller ischemic area is the result of more distal thrombus location and a good collateral status.

Interestingly, none of the patients with an intra-cranial internal carotid artery occlusion showed complete reperfusion. Patients selected in this study were treated with intra-venous thrombolysis only, and this supports the consideration of intra-arterial treatment in patients with an intra-cerebral internal carotid artery occlusion.

## Blood-brain barrier permeability measurements (Patlak model) with CTP in acute ischemic stroke patients

Blood-brain barrier permeability has been related to the occurrence of hemorrhagic transformation and malignant edema and could therefore be a valuable tool in predicting these complications.[24] Blood-brain barrier permeability can be calculated from extended acquisition CTP by mathematical abstraction of the perfusion process of leakage of contrast out of the cerebral vessels.[25] To gain insight into the meaning of blood-brain barrier measurements the relationship between patient characteristics, stroke severity and blood-brain permeability values, as well as the reproducibility of these measurements, needs to be investigated before blood-brain barrier permeability can be used in a clinical setting.

In **chapter 3** it is shown that only early CT signs of ischemia on non-contrast CT (NCCT) are related to higher blood-brain barrier permeability values in the infarct core when measured with the Patlak model.[2] This implies that only severe ischemic changes alter the blood-brain barrier permeability within the first hours after stroke onset. Another finding was that there were no significant differences between the median blood-brain barrier permeability values found in penumbra, infarct core and unaffected contralateral hemisphere. Interestingly, the permeability values found in the unaffected contralateral hemisphere were not zero. These findings suggest that the measurements are largely influenced by noise and raises serious concerns about the use of the Patlak model in detecting blood-brain barrier permeability.

A new method of calculating blood-brain barrier permeability was therefore developed, using information of the entire attenuation curve instead of only the first pass steady state data.[26] This method was used in the other studies investigating permeability in this thesis.



## Reperfusion, blood-brain barrier permeability (nonlinear regression, NLR model) and hemorrhagic transformation

Intra-venous thrombolysis increases the risk of hemorrhagic transformation by its influence on the clotting system. In addition, reperfusion and blood-brain barrier permeability have

both also been associated with hemorrhagic transformation.[21, 27-29] It is unclear whether hemorrhagic transformation occurs secondary to the combination of reperfusion and ischemic injury to the blood-brain barrier, or it is caused by the negative effect of intra-venous recombinant tissue Plasminogen Activator on the blood-brain barrier integrity.

The results of the study in **chapter 4**, investigating the relation between reperfusion and the occurrence of hemorrhagic transformation, did not show an association between these two variables, irrespective of whether patients were treated with intra-venous thrombolysis or not.[3] Because the percentage of hemorrhagic transformation was higher in the patients treated with intra-venous thrombolysis, the results suggests that the delivery of recombinant tissue Plasminogen Acivator to the ischemic area with possible direct injury to the blood-brain barrier, and not reperfusion itself, results in hemorrhagic transformation.

The new method of calculating blood-brain barrier permeability and the prediction of hemorrhagic transformation was tested in a small patient group of 60 patients in **chapter 5**, and compared the nonlinear regression method with the standard (and fixed offset) Patlak model.[5] The highest discriminating power was found for relative permeability surface (rPS) area product measurements obtained with nonlinear regression. The area under the curve (AUC) of the receiver operator characteristics (ROC) analysis for rPS predicting hemorrhagic transformation was 0.75, with a sensitivity of 0.75 and a specificity of 0.75. The maximum AUC of the Patlak based methods was 0.67.

Building on these results, in **chapter 6**, the added predictive value of this nonlinear regression permeability method was tested in all patients in the Dutch acute stroke study (DUST) population that received intra-venous thrombolysis or intra-arterial treatment, and at risk for developing hemorrhagic transformation.[4] Although nonlinear regression permeability did show a positive association with the occurrence of hemorrhagic transformation, it did not improve prediction of hemorrhagic transformation compared to prediction with age and admission NIHSS.

## Reperfusion, blood-brain barrier permeability (NLR model) and malignant edema

Severe brain swelling in large middle cerebral artery infarcts, with midline shift and neurological deterioration, has a high morbidity and mortality rate.[30-32] It is unclear why some patients with large middle cerebral artery infarcts develop this severe swelling while others do not. Understanding which variables are involved in its development could help to predict its occurrence and provide targets for future early treatment options.

In **chapter 7**, a study including patients with large middle cerebral artery infarcts on follow-up, it was found that more early CT signs of infarction on NCCT, more proximal thrombus location, higher clot burden and poor collateral score on CTA, and larger cerebral blood volume (CBV) deficit size and higher permeability estimates on CTP are all associated

with severe brain swelling.[6] Although clot extent can change over time, this suggests that patients who develop this severe swelling already have a proximal clot and poor collaterals on admission, which leads to a larger affected area and increased permeability. In patients without swelling the occlusion is probably located more distally initially, but may extend more proximally with time. Interestingly, no significant association was found with intra-venous thrombolysis treatment, recanalization or reperfusion. Together with the finding that there was also no difference in time from onset to scan series, the stroke severity at arrival at the hospital seems to be the most important clinical factor leading to the occurrence of severe edema. Reduction in morbidity and mortality associated with space-occupying cerebral edema in patients with middle cerebral artery strokes could therefore possibly be achieved by an even earlier identification of patients at risk and start of intra-arterial treatment.

In **chapter 8** the new method of calculating blood-brain barrier permeability was assessed for its predictive value for malignant edema in a population of patients with a proximal middle cerebral artery occlusion, and considered to be at risk for developing malignant edema.[7] It was found that nonlinear regression permeability is an early predictor of malignant edema and that it improves prediction together with clot burden score (AUC 0.80) and collateral score (AUC 0.76), with a final high AUC of 0.88.

Although hemicraniectomy has been shown to reduce mortality and improve functional outcome, the results are limited if extensive damage due to malignant cerebral edema has already occurred. Our findings suggest the new method of calculating blood-brain barrier permeability could be used in the evaluation and decision making process for patients at risk of developing malignant edema, and has the potential to improve outcome by earlier selection of patients for treatment with hemicraniectomy.

# General discussion

The outcome of patients with acute ischemic stroke is determined by the initial severity of the stroke, the time to treatment and the occurrence of severe complications like hemorrhagic transformation and malignant edema. The effect of treatment on favorable outcome is relatively minor with the number needed to treat ranging from four to 19 for intra-venous thrombolysis, with a higher number if treatment is started later.[33] For patients with an occlusion of one of the larger sized arteries, intra-arterial thrombectomy can be performed with a the number needed to treat to achieve an favorable outcome of around four.[33-35] This means that a large majority of patients will not benefit from the treatment they receive.



## Patient selection for treatment

An important problem is that hemorrhagic transformation can occur spontaneously after acute ischemic stroke, but also as a consequence of treatment. Interestingly, despite the

increased number of patients with hemorrhagic transformation in the earlier randomized trials, the incidence of hemorrhagic transformation after intra-venous thrombolysis has not changed much during the last decade.[36] This might be explained by a reduction in the risk of spontaneous hemorrhagic transformation related to vessel damage due to ischemia (thanks to the increased stroke awareness and earlier treatment), and by an increase in the risk caused by intra-venous thrombolysis or intra-arterial thrombectomy. As a consequence, the individual patient having hemorrhagic transformation could have changed.

The appropriate selection of patients for treatment is therefore crucial to improve the contribution of current treatment strategies to outcome. The main challenge remains in identifying which patients will not benefit, or are at a higher risk of complications with treatment, and which ones will benefit, or are at a higher risk of complications without treatment.[16] By being able to identify patients at risk for complications and knowing what causes these complications, both the acute stroke treatment and preventive treatment for these complications can be tailored to the individual patient to improve outcome.

An important predictor of outcome is the stroke severity on arrival in the emergency department. Selection of patients for treatment is however largely based on time since treatment onset. Imaging variables like the presence of collateral blood supply, Alberta Stroke Program Early CT Score (ASPECTS) on NCCT, the amount of ischemic tissue assessed with CTP, or the damage to the blood-brain barrier may provide a better estimate of the risk of developing severe complications with treatment.

Imaging assessment of acute stroke patients has changed with the emergence of intra-arterial thrombectomy. In previous stroke protocols only a NCCT was required to rule out hemorrhage or tumor as cause of neurological symptoms, and intra-venous thrombolysis was started after this scan. At present, it is common practice to acquire a CTA for the assessment of the clot location, clot burden and collaterals in order to decide whether additional intra-arterial treatment should be given and to plan this procedure.[11]

## CT perfusion imaging.

The addition of CTP for the assessment of acute ischemic stroke patients is still under debate. In the current guidelines the advice is not to perform standard CTP scans, mainly because of insufficient evidence supporting its use.[37] This will probably cause many centers to omit CTP imaging. However, CTP probably can provide useful information, while the time needed and financial costs are low. The potential delay to treatment could be reduced to zero if intra-venous thrombolysis is started in the scanner room immediately after the NCCT is performed, and before the additional CTA and CTP scans are done. This is already the successful practice in some stroke centers in The Netherlands. Although a direct association between CTP derived parameters and its ability to improve intra-arterial thrombectomy outcome has not been sufficiently established, information on infarct core and penumbra

size and location could aid clinical decision making, especially in specific and difficult cases. Rapid transfer of CTP images from smaller district hospitals, with e.g. the RAPID software, helps in quickly disseminating vital information with color-coded images to the interventional radiologist on call at the major stroke center.[38] CTP has been shown to have a high sensitivity and very high specificity for detection of infarcts, and a significant additional diagnostic value for detecting ischemic changes in posterior circulation stroke.[39, 40] Additionally, NCCT and dynamic CTA data can be easily extracted from CTP data using the same contrast bolus, which obviates the need for a further scan series, providing the coverage of future scanners will be able to include the arch vessels in the same series.[41, 42] Estimates of blood-brain barrier permeability can also be obtained with CTP.[26]

## Blood-brain barrier permeability imaging with CTP and stroke complications

In this thesis it was attempted to use CTP derived measurements of blood-brain barrier permeability and reperfusion to understand and predict the development of hemorrhagic transformation and malignant edema in acute ischemic stroke patients. It was shown that hemorrhagic transformation seems to be the result of intra-venous thrombolysis itself, and is not related to reperfusion.[3] In addition, it was shown that hemorrhagic transformation can be predicted with CTP-derived blood-brain barrier permeability measurements.[4] For the occurrence of the other major complication, malignant edema, the results show that the stroke severity on arrival seems to play the largest role.[6] Blood-brain barrier permeability proved to be an independent predictor of malignant edema and could therefore potentially be used to select patients for preventive hemicraniectomy.[7]

Interestingly, blood-brain barrier permeability measurements were more useful for the prediction of cerebral edema than for predicting hemorrhage. Two possible reasons for the better performance of blood-brain barrier permeability in predicting malignant edema compared to hemorrhagic transformation are (1) the size of the gaps in the blood-brain barrier in relation to size of the leaking substance, and (2) the presumed more focal origin of hemorrhagic transformation. The vasogenic component of cerebral edema formation implies that there is movement of water molecules from the intra-vascular to the extra-vascular compartment, whilst the occurrence of hemorrhagic transformation depends on the transfer of, much larger sized, erythrocytes through the leaking blood-brain barrier. It is probably easier to detect generalized smaller sized disturbances of the blood-brain barrier than to find a larger much more focal damage in the blood-brain barrier. Additionally, it is conceivable that the larger openings leading to hemorrhagic transformation (complete vessel wall disruption) only occur at a specific location and only at the moment of hemorrhagic transformation (whether or not influenced by the effects of intra-venous thrombolysis), and are not present at an earlier time. The specific location, where hemorrhagic transformation starts initially, is often obscured by the mass effect of the hematoma. Not knowing this

location makes deciding where to measure blood-brain barrier permeability challenging. This makes blood-brain barrier measurements possibly less suitable for predicting hemorrhagic transformation.

Moreover, measuring contrast in the completely occluded territory is difficult, and it might therefore be better to focus the BBBP measurement on the penumbra, which still receives some blood flow and hence should give more reliable BBBP measurements. Especially, permeability changes at the gradual inter-phase from penumbra to infarct core could be of use.

Other methods to improve BBBP measurement are enhancement of the detector calibration to reduce ring shaped scanner artifacts and the use of more sophisticated iterative reconstruction techniques.[5] Improving blood-brain barrier measurements could improve its diagnostic value for the prediction of complications in acute ischemic stroke. Additionally, increased axial coverage to full brain coverage, extraction of angiography data from CT perfusion data could improve the diagnostic yield.

## Reperfusion assessment with CTP and stroke complications

Besides the evaluation of acute stroke patients on admission, CTP can also used to monitor the treatment effect. Our understanding of the modest contribution of treatment on outcome may improve by visualizing the early effect of the applied treatment. With sequential CTP images the reperfusion of the affected tissue can be evaluated. The results of this thesis have shown that reperfusion seems to be an appropriate additional tool for this purpose. Evaluating reperfusion would most likely be more useful during treatment. With intra-arterial treatment this could be achieved by improving the quality of flatpanel CTP in the interventional suite. These images could be used to better identify areas that are still ischemic from residual thrombus in the smaller capillaries after intra-arterial thrombectomy. It is conceivable that further miniaturization of interventional equipment would help to treat even more distal thrombi in smaller arteries, supplying e.g. vital areas like Broca and Wernicke.

## Stroke care organization

Improvement of the way stroke care is organized could further improve stroke outcome. Stroke awareness has increased in the last 10 years and patients present much earlier, which has a great effect on outcome. The recent emergence of intra-arterial thrombectomy for large artery occlusions, thanks to a large number of randomized clinical trials with a positive outcome, is a major step forward. Because of these changes, the need for an even more comprehensive national stroke service, including Interventional Radiology services, is paramount. Consensus criteria for the development of these services have been published recently.[43, 44]

## Stroke care funding

Funding of these new treatments is another important issue which needs to be resolved. In some countries, like The Netherlands, some (but still insufficient) funding has been awarded by the government agencies. In other countries, like the United Kingdom, no specific funding has yet been allocated to develop these services despite recommendations in the national guidelines.[45] This could be a major concern for the outcome of future stroke patients.

# Conclusions

Imaging is a crucial part of the care of acute ischemic stroke patients. It can be used for the initial patient evaluation, treatment selection, treatment monitoring, complication prediction, and outcome prediction. CT can provide fast and easy imaging of patients and most of the necessary information can be derived from CTP, although this technique needs further improvement before it can become standard clinical practice.

# References


1. Horsch AD, Dankbaar JW, Niesten JM, van Seeters T, van der Schaaf IC, van der Graaf Y, Mali WP, Velthuis BK. Predictors of Reperfusion in Patients with Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2015;36:1056-1062

2. Horsch AD, Dankbaar JW, van Seeters T, Niesten JM, Luitse MJ, Vos PC, van der Schaaf IC, Biessels GJ, van der Graaf Y, Kappelle LJ, Mali WP, Velthuis BK. Relation between stroke severity, patient characteristics and CT-perfusion derived blood-brain barrier permeability measurements in acute ischemic stroke. Clin Neuroradiol. 2015 Feb 27

3. Horsch AD, Dankbaar JW, van der Graaf Y, Niesten JM, van Seeters T, van der Schaaf IC, Kappelle LJ, Velthuis BK. Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke. Neuroradiology. 2015;57:1219-1225

4. Horsch AD, Bennink E, Van Seeters T, Kappelle LJ, van der Graaf Y, Mali WP, de Jong HW, Velthuis B, Dankbaar JW. Can blood-brain barrier CT perfusion derived permeability measurements predict hemorrhagic transformation in acute ischemic stroke? Manuscript

5. Bennink E, Horsch AD, Dankbaar JW, Velthuis BK, Viergever MA, de Jong HW. CT perfusion analysis by nonlinear regression for predicting hemorrhagic transformation in ischemic stroke. Medical physics. 2015;42:4610-4618

6. Horsch AD, Dankbaar JW, Stemerdink TA, Bennink E, van Seeters T, Kappelle LJ, Hofmeijer J, de Jong HW, van der Graaf Y, Velthuis BK. Imaging Findings Associated with Space-Occupying Edema in Patients with Large Middle Cerebral Artery Infarcts. AJNR Am J Neuroradiol 2016;37:831-837

7. Horsch AD, Velthuis BK, Bennink E, De Jong HW, Stemerdink TA, van der Worp HB, Kappelle LJ, hofmeijer J, Y van der Graaf, Mali WP, Dankbaar JW. Blood-brain barrier permeability measurements with CT perfusion predict prominent edema in acute ischemic stroke. Submitted

8. NINDS rssg. 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;333:1581-1587

9. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275-282

10. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-1329

11. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA,

Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11-20

12. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009-1018

13. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019-1030

14. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallofre M, Davalos A. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296-2306

15. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285-2295

16. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke. 2012;43:2904-2909

17. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. Cerebrovasc Dis. 2008;25:176-184

18. Saver JL. Time is brain--quantified. Stroke. 2006;37:263-266

19. Wintermark M, Albers GW, Broderick JP, Demchuk AM, Fiebach JB, Fiehler J, Grotta JC, Houser G, Jovin TG, Lees KR, Lev MH, Liebeskind DS, Luby M, Muir KW, Parsons MW, von Kummer R, Wardlaw JM, Wu O, Yoo AJ, Alexandrov AV, Alger JR, Aviv RI, Bammer R, Baron JC, Calamante F, Campbell BC, Carpenter TC, Christensen S, Copen WA, Derdeyn CP, Haley EC, Jr., Khatri P,

Kudo K, Lansberg MG, Latour LL, Lee TY, Leigh R, Lin W, Lyden P, Mair G, Menon BK, Michel P, Mikulik R, Nogueira RG, Ostergaard L, Pedraza S, Riedel CH, Rowley HA, Sanelli PC, Sasaki M, Saver JL, Schaefer PW, Schellinger PD, Tsivgoulis G, Wechsler LR, White PM, Zaharchuk G, Zaidat OO, Davis SM, Donnan GA, Furlan AJ, Hacke W, Kang DW, Kidwell C, Thijs VN, Thomalla G, Warach SJ. Acute Stroke Imaging Research Roadmap II. Stroke. 2013;44:2628-2639

20. Dalkara T, Arsava EM. Can restoring incomplete microcirculatory reperfusion improve stroke outcome after thrombolysis? J Cereb Blood Flow Metab. 2012;32:2091-2099

21. Molina CA, Alvarez-Sabin J. Recanalization and reperfusion therapies for acute ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl 1:162-167

22. del Zoppo GJ. Virchow's triad: the vascular basis of cerebral injury. Rev Neurol Dis. 2008;5 Suppl 1:S12-21

23. Wong CH, Crack PJ. Modulation of neuro-inflammation and vascular response by oxidative stress following cerebral ischemia-reperfusion injury. Curr Med Chem. 2008;15:1-14

24. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, Lau BC, Smith W, Dillon WP, Wintermark M. Blood-Brain Barrier Permeability Assessed by Perfusion CT Predicts Symptomatic Hemorrhagic Transformation and Malignant Edema in Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2011;32:41-48

25. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab. 1983;3:1-7

26. Bennink E, Riordan AJ, Horsch AD, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. J Cereb Blood Flow Metab. 2013;33:1743-1751

27. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol. 2006;60:508-517

28. Fiehler J, Remmele C, Kucinski T, Rosenkranz M, Thomalla G, Weiller C, Zeumer H, Rother J. Reperfusion after severe local perfusion deficit precedes hemorrhagic transformation: an MRI study in acute stroke patients. Cerebrovasc Dis. 2005;19:117-124

29. Warach S. Evidence of Reperfusion Injury, Exacerbated by Thrombolytic Therapy, in Human Focal Brain Ischemia Using a Novel Imaging Marker of Early Blood-Brain Barrier Disruption. Stroke. 2004;35:2659-2661

30. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53:309-315

31. Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. Intensive Care

Med. 1998;24:620-623

32. Heinsius T, Bogousslavsky J, Van Melle G. Large infarcts in the middle cerebral artery territory. Etiology and outcome patterns. Neurology. 1998;50:341-350

33. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. Stroke. 2009;40:2079-2084

34. Saver JL, Gornbein J, Grotta J, Liebeskind D, Lutsep H, Schwamm L, Scott P, Starkman S. Number needed to treat to benefit and to harm for intravenous tissue plasminogen activator therapy in the 3- to 4.5-hour window: joint outcome table analysis of the ECASS 3 trial. Stroke. 2009;40:2433-2437

35. Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, Roy D, Thornton J, Dorado L, Bonafe A, Levy EI, Diener HC, Hernandez-Perez M, Pereira VM, Blasco J, Quesada H, Rempel J, Jahan R, Davis SM, Stouch BC, Mitchell PJ, Jovin TG, Saver JL, Goyal M. Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials. Stroke. 2016;47:798-806

36. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke. 2003;34:2847-2850

37. Nederlands Vereniging voor Neurologie. Conceptrichtlijn Herseninfarct en hersenbloeding. 2016

38. Straka M, Albers GW, Bammer R. Real-time diffusion-perfusion mismatch analysis in acute stroke. J Magn Reson Imaging. 2010;32:1024-1037

39. Biesbroek JM, Niesten JM, Dankbaar JW, Biessels GJ, Velthuis BK, Reitsma JB, van der Schaaf IC. Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2013;35:493-501

40. van der Hoeven EJ, Dankbaar JW, Algra A, Vos JA, Niesten JM, van Seeters T, van der Schaaf IC, Schonewille WJ, Kappelle LJ, Velthuis BK. Additional diagnostic value of computed tomography perfusion for detection of acute ischemic stroke in the posterior circulation. Stroke. 2015;46:1113-1115

41. Smit EJ, Vonken EJ, van der Schaaf IC, Mendrik AM, Dankbaar JW, Horsch AD, van Seeters T, van Ginneken B, Prokop M. Timing-Invariant Reconstruction for Deriving High-Quality CT Angiographic Data from Cerebral CT Perfusion Data. Radiology. 2012;263(1):216-225

42. Smit EJ, Vonken EJ, van Seeters T, Dankbaar JW, van der Schaaf IC, Kappelle LJ, van Ginneken B, Velthuis BK, Prokop M. Timing-invariant imaging of collateral vessels in acute ischemic stroke. Stroke. 2013;44:2194-2199

43. Lavine SD, Cockroft K, Hoh B, Bambakidis N, Khalessi AA, Woo H, Riina H, Siddiqui A, Hirsch JA, Chong W, Rice H, Wenderoth J, Mitchell P, Coulthard A, Signh TJ, Phatorous C, Khangure M, Klurfan P, Ter Brugge K, Iancu D, Gunnarsson T, Jansen O, Muto M, Szikora I, Pierot L, Brouwer P, Gralla J, Renowden S, Andersson T, Fiehler J, Turjman F, White P, Januel AC, Spelle L,

Kulcsar Z, Chapot R, Biondi A, Dima S, Taschner C, Szajner M, Krajina A, Sakai N, Matsumaru Y, Yoshimura S, Ezura M, Fujinaka T, Iihara K, Ishii A, Higashi T, Hirohata M, Hyodo A, Ito Y, Kawanishi M, Kiyosue H, Kobayashi E, Kobayashi S, Kuwayama N, Matsumoto Y, Miyachi S, Murayama Y, Nagata I, Nakahara I, Nemoto S, Niimi Y, Oishi H, Satomi J, Satow T, Sugiu K, Tanaka M, Terada T, Yamagami H, Diaz O, Lylyk P, Jayaraman MV, Patsalides A, Gandhi CD, Lee SK, Abruzzo T, Albani B, Ansari SA, Arthur AS, Baxter BW, Bulsara KR, Chen M, Almandoz JE, Fraser JF, Heck DV, Hetts SW, Hussain MS, Klucznik RP, Leslie-Mawzi TM, Mack WJ, McTaggart RA, Meyers PM, Mocco J, Prestigiacomo CJ, Pride GL, Rasmussen PA, Starke RM, Sunenshine PJ, Tarr RW, Frei DF, Ribo M, Nogueira RG, Zaidat OO, Jovin T, Linfante I, Yavagal D, Liebeskind D, Novakovic R, Pongpech S, Rodesch G, Soderman M, Taylor A, Krings T, Orbach D, Picard L, Suh DC, Zhang HQ. Training guidelines for endovascular stroke intervention: an international multi-society consensus document. Neuroradiology. 2016;58:537-541

44. Lavine SD, Cockroft K, Hoh B, Bambakidis N, Khalessi AA, Woo H, Riina H, Siddiqui A, Hirsch JA, Chong W, Rice H, Wenderoth J, Mitchell P, Coulthard A, Signh TJ, Phatorous C, Khangure M, Klurfan P, terBrugge K, Iancu D, Gunnarsson T, Jansen O, Muto M, Szikora I, Pierot L, Brouwer P, Gralla J, Renowden S, Andersson T, Fiehler J, Turjman F, White P, Januel AC, Spelle L, Kulcsar Z, Chapot R, Biondi A, Dima S, Taschner C, Szajner M, Krajina A, Sakai N, Matsumaru Y, Yoshimura S, Ezura M, Fujinaka T, Iihara K, Ishii A, Higashi T, Hirohata M, Hyodo A, Ito Y, Kawanishi M, Kiyosue H, Kobayashi E, Kobayashi S, Kuwayama N, Matsumoto Y, Miyachi S, Murayama Y, Nagata I, Nakahara I, Nemoto S, Niimi Y, Oishi H, Satomi J, Satow T, Sugiu K, Tanaka M, Terada T, Yamagami H, Diaz O, Lylyk P, Jayaraman MV, Patsalides A, Gandhi CD, Lee SK, Abruzzo T, Albani B, Ansari SA, Arthur AS, Baxter BW, Bulsara KR, Chen M, Delgado Almandoz JE, Fraser JF, Heck DV, Hetts SW, Hussain MS, Klucznik RP, Leslie-Mawzi TM, Mack WJ, McTaggart RA, Meyers PM, Mocco J, Prestigiacomo CJ, Pride GL, Rasmussen PA, Starke RM, Sunenshine PJ, Tarr RW, Frei DF, Ribo M, Nogueira RG, Zaidat OO, Jovin T, Linfante I, Yavagal D, Liebeskind D, Novakovic R, Pongpech S, Rodesch G, Soderman M, Taylor A, Krings T, Orbach D, Picard L, Suh DC, Zhang HQ. Training Guidelines for Endovascular Ischemic Stroke Intervention: An International Multi-Society Consensus Document. AJNR Am J Neuroradiol. 2016;37:E31-34

45. NICE. Mechanical clot retrieval for treating acute ischaemic stroke. Interventional procedure guidance. IPG548. 2016

# CHAPTER 9

## Summary and general discussion
## Samenvatting

# Samenvatting

## Acuut herseninfarct

Een acuut herseninfarct is het gevolg van een afsluiting van een aanvoerend bloedvat naar een deel van de hersenen, meestal door een bloedstolsel. Al direct na het ontstaan van een afsluiting komen er te weinig voedingsstoffen en zuurstof bij de hersencellen waardoor deze niet goed kunnen functioneren en symptomen ontstaan, zoals bijvoorbeeld praatstoornissen en verlammingen. Dit wordt 'ischemie' genoemd. Als de afsluiting snel wordt opgeheven is er grote kans dat er geen blijvende schade is, maar als de afsluiting langer duurt dan sterven de hersencellen af en is de schade definitief. Het gebied waar de schade definitief is wordt 'infarct' genoemd en het gebied dat spontaan of met behandeling nog gered kan worden, 'penumbra'. Snelle diagnose en behandeling zijn van groot belang omdat er dan minder definitieve schade is.

## Behandeling

Het doel van het behandelen van een acuut herseninfarct is het oplossen of verwijderen van het bloedstolsel. Er zijn hiervoor 2 soorten behandeling beschikbaar. Ten eerste is er de intra-veneuze thrombolyse ('IVT') waarbij een bloedverdunner ('rtPA', recombinant tissue Plasminogen Activator) met een infuus in een ader wordt ingespoten. Deze stroomt dan door alle vaten in het lichaam en dus ook naar de slagader met een afsluiting. Het is bewezen dat deze behandeling werkzaam kan zijn tot 4.5 uur na het begin van de symptomen en met name bij kleinere afsluitingen. Sinds kort is er een tweede methode, intra-arteriële thrombectomie ('IAT'), waarbij via toegang in een slagader in de lies een katheter naar de plaats van de afsluiting wordt gebracht en het bloedstolsel wordt verwijderd door opzuigen of met behulp van een speciale stent van zijn plaats wordt getrokken. Deze behandeling is met name van belang bij afsluitingen in grotere vaten en wordt toegepast tot 6 uur (soms zelfs langer) na begin van de symptomen.

## Beeldvorming

Patiënten die op de eerste hulp binnenkomen en symptomen vertonen die kunnen passen bij een acuut herseninfarct worden onderzocht met beeldvorming. In de meeste ziekenhuizen gebeurt dit met CT-scanners. In de eerste plaats wordt er een scan gemaakt zonder contrast (blanco CT) om andere diagnoses zoals bloeding of tumor aan te tonen of uit te sluiten. Het is belangrijk om een bloeding uit te sluiten omdat de behandeling met bloedverdunners bij patiënten die al een bloeding hebben gevaarlijk is. In toenemende mate worden er ook scans gedaan waarbij contrast in de bloedvaten wordt geïnjecteerd. CT-angiografie (CTA) geeft informatie over de grotere bloedvaten, en met name over de uitgebreidheid (clot burden score, CBS) en plaats van een afsluiting en over de aanwezigheid van alternatieve routes (collateralen) voor bloedaanvoer naar het aangedane gebied (collateraal score). Dit

geeft informatie die onder andere van belang is voor de besluitvorming over de planning van een IAT. Een tweede soort contrast scan is CT-perfusie (CTP). Deze geeft informatie over de doorbloeding en schade op weefselniveau. Hierbij wordt doorstroming van contrast door de hersenen over de tijd gemeten. Parameters die hiermee verkregen worden zijn bloeddoorstroming (cerebral blood flow, CBF), bloed volume (cerebral blood volume, CBV), gemiddelde doorstroomtijd (mean transit time, MTT) en tijd tot maximum (time to peak, TTP). Een relatief nieuwe parameter die ook met CTP bepaald kan worden is bloed-hersen barrière permeabiliteit (BBBP).

Deze CTA en CTP contrast scans zijn in het kader van de Dutch acute stroke study (DUST), een groot onderzoek in 14 ziekenhuizen in Nederland bij bijna 1500 patiënten met het vermoeden van een acuut herseninfarct, gemaakt bij binnenkomst op de eerste hulp (en bij een deel ook als controle scan na 3 dagen). Het doel van dit onderzoek was de toegevoegde waarde van de CTA en CTP bij het voorspellen van de uitkomst in deze patiëntengroep te bepalen. Alle studies in dit proefschrift zijn gebaseerd op de data van de DUST.

## Bloed-hersen barrière permeabiliteit (BBBP)

De bloed-hersen barrière reguleert het transport door de wand van de bloedvaatjes (capillairen) in de hersenen. Als gevolg van de occlusie krijgen ook deze kleine bloedvaatjes in het hersenweefsel te weinig voedingstoffen en zuurstof waardoor deze beschadigd raken en kunnen gaan lekken. Dit wordt permeabiliteit genoemd. Deze permeabiliteit kan worden geschat met CTP waarbij de lekkage van contrast in het weefsel rond de bloedvaten wordt gemeten. Hoewel er verschillende studies gepubliceerd zijn over de relatie tussen permeabiliteit en ernstige complicaties zoals een bloeding (hemorrhagische transformatie) en hersenzwelling is er nog veel onduidelijk. Zo is de duur van de scan van belang en zijn ook de gebruikte software modellen van invloed op de resultaten. Een veel gebruikte methode voor het berekenen van permeabiliteit is het Patlak model. Dit model is echter gevoelig voor kleine fluctuaties in de sterkte van het signaal en de ruis. Daarom is er een nieuwe methode voor het analyseren van de permeabiliteit ontwikkeld in ons ziekenhuis. Deze methode gaat uit van een ander natuurkundig model (nonlineaire regressie, NLR) en geeft meer betrouwbare waarden vergeleken met het Patlak model.

## Reperfusie en recanalisatie

Het belangrijkste doel van IVT en IAT is het herstellen van de bloedtoevoer naar het aangedane gebied. Dit wordt revascularisatie genoemd. Revascularisatie kan worden onderverdeeld in 3 componenten: (1) recanalisatie van de afgesloten slagader; (2) rekrutering van collateralen; en (3) reperfusie, dat wil zeggen revascularisatie van de hersencapillairen. De termen reperfusie en recanalisatie worden in de literatuur vaak door elkaar gebruikt. Dit kan echter tot verwarring leiden omdat recanalisatie niet noodzakelijkerwijs tot reperfusie en een betere uitkomst leidt. Recanalisatie kan bepaald worden met CTA en reperfusie met CTP

als controle scans.

## Complicaties

Twee ernstige complicaties die kunnen optreden na een acuut herseninfarct zijn een bloeding in het infarct ('hemorrhagische transformatie', HT) en hersenzwelling ('maligne oedeem', ME).

Een bloeding in het infarct kan spontaan optreden, ook als er geen behandeling wordt gegeven, maar het risico is hoger bij behandeling met IVT of IAT. Een van de belangrijke onderwerpen in dit proefschrift is het van tevoren kunnen voorspellen (voordat behandeling is gegeven), welke patiënt een bloeding zal ontwikkelen zodat de risico's en de kans op succes beter tegen elkaar afgewogen kunnen worden. Informatie over de permeabiliteit zou hier een belangrijke rol bij kunnen spelen.

Bij het optreden van de andere complicatie, de hersenzwelling, kan er een verhoogde hersendruk ontstaan. Deze kan leiden tot een vicieuze cirkel doordat de verhoogde hersendruk de doorbloeding van de hersenen tegenwerkt. De hersenzwelling komt vooral voor bij grote infarcten in het gebied van de middelste hersenarterie. De enige behandeling die momenteel beschikbaar is, is het verwijderen van een deel van de schedel (hemi-craniectomie) zodat de hersenen ruimte krijgen om te zwellen en de doorbloeding niet wordt tegengewerkt. Het is belangrijk dat deze operatie vroeg genoeg wordt uitgevoerd om de vicieuze cirkel te voorkomen, maar het is vooralsnog moeilijk te voorspellen wie hersenzwelling gaat ontwikkelen en wie niet. De gedachte is dat permeabiliteit ook bij de ontwikkeling van hersenzwelling een belangrijke rol speelt.

## Dit proefschrift

In dit proefschrift worden relaties tussen 4 belangrijke factoren die van invloed zijn op de uitkomst van patiënten met een herseninfarct onderzocht. Reperfusie, permeabiliteit, hemorrhagische transformatie en maligne oedeem.

In **hoofdstuk 2** is de relatie tussen recanalisatie en reperfusie onderzocht. De resultaten laten zien dat er een sterke relatie is tussen recanalisatie en reperfusie maar dat complete reperfusie mogelijk is ondanks incomplete recanalisatie en vice versa. Dit suggereert dat het nuttig kan zijn om zowel recanalisatie als reperfusie te beoordelen ter evaluatie van de volledigheid van een behandeling. In deze studie werd ook gekeken naar voorspellers van complete reperfusie. Een kleiner ischemisch gebied bij binnenkomst bleek de enige onafhankelijke voorspeller van complete reperfusie. Dit is niet verrassend aangezien een kleiner ischemisch gebied gerelateerd is aan een afsluiting in een van de kleinere slagaders en betere collateralen. Een derde bevinding van deze studie is dat geen van de patiënten met een bloedstolsel in het intracraniele deel (in de schedel) van de carotis interna (een van de grote vaten naar de hersenen) complete reperfusie vertoonde na behandeling met alleen IVT. Dit bevestigt dat patiënten

met een afsluiting van een van de grotere slagaders meer gebaat zijn bij IAT.

In **hoofdstuk 3** is de relatie tussen patiënt karakteristieken, ernst van het herseninfarct en permeabiliteit gemeten met het Patlak model onderzocht. Hieruit bleek dat alleen vroege tekenen van ischemie op een blanco CT (early CT signs of ischemia, ECTS) gerelateerd zijn aan een verhoogde permeabiliteit in het infarct en dit suggereert dat alleen ernstige ischemische schade de permeabiliteit verandert in de eerste uren na binnenkomst. Andere bevindingen waren dat er geen belangrijke verschillen gevonden zijn tussen de waarden in de penumbra of het infarct in de aangedane en niet aangedane hersenhelft. Ook was de permeabiliteit in de niet aangedane hersenhelft niet nul. Deze bevindingen suggereren dat de metingen sterk beïnvloed worden door ruis en stellen vraagtekens bij de bruikbaarheid van het Patlak model. Daarom is een nieuw model ontwikkeld dat gebruikt is in de overige studies in dit proefschrift.

In **hoofdstuk 4** is de relatie onderzocht tussen reperfusie en bloeding in het infarct. IVT beïnvloedt het risico op bloeding door beïnvloeding van het stollingssysteem maar rtPA kan ook directe schade aan de bloed-hersen barrière veroorzaken. Daarnaast worden zowel reperfusie als permeabiliteit in de literatuur als risicofactoren voor bloeding genoemd. Het is onduidelijk of een bloeding in het infarct het gevolg is van de combinatie van reperfusie van een deel van het brein met schade aan de bloedvaten en daardoor verhoogde permeabiliteit of dat deze een effect is van schade aan de bloed-hersen barrière veroorzaakt door rtPA. De resultaten van dit hoofstuk tonen geen relatie tussen reperfusie en het optreden van een bloeding, ongeacht of patiënten behandeld waren met IVT. Wel was het percentage patiënten met bloedingen hoger in de behandelde groep patiënten. Dit suggereert dat de invloed van rtPA op de permeabiliteit en niet de reperfusie gerelateerd is aan het ontstaan van een bloeding in het infarct.

De nieuwe methode om permeabiliteit te meten is onderzocht in een kleine groep van 60 patiënten in **hoofdstuk 5**. Het beste onderscheidende vermogen om een bloeding te voorspellen is gevonden voor de parameter: relative permeability surface area product (rPS). Deze parameter is vervolgens getest in **hoofdstuk 6** op alle patiënten in de DUST-database die behandeld zijn met IVT of IAT. De resultaten laten zien dat de permeabiliteit gemeten met de nieuwe methode een bloeding in het infarct kan voorspellen, maar dat deze in vergelijking met andere voorspellers van bloeding zoals leeftijd en ernst van de symptomen (gemeten met de National Institutes of Health Stroke Scale, NIHSS) de voorspellende waarde niet beter maakt.



Omdat het nog onduidelijk is waarom sommige patiënten met een groot infarct op controle scans hersenzwelling ontwikkeld hebben en andere niet, hebben we in **hoofdstuk 7** onderzocht welke factoren gerelateerd zijn aan het optreden van zwelling. De bevindingen waren dat ernstigere tekenen van infarct op blanco CT (ECTS), een afsluiting van een van de grotere slagaders, een grotere omvang van het bloedstolsel en slechtere collateralen op CTA,

en een groter infarct en verhoogde permeabiliteit verkregen met CTP allen gerelateerd zijn aan het optreden van hersenzwelling. Dit suggereert dat patiënten die zwelling ontwikkelen bij binnenkomst al een uitgebreider bloedstolsel in een grotere slagader met slechtere collateralen hebben, hetgeen een groter aangedaan gebied en verhoogde permeabiliteit tot gevolg heeft. Ook suggereren de resultaten dat patiënten die geen zwelling ontwikkelen in eerste instantie een kleinere hoeveelheid bloedstolsel en een kleiner aangedaan gebied hebben maar dat dit vervolgens langzaam groter wordt. Verrassend genoeg werd er geen relatie gevonden tussen hersenzwelling en behandeling met IVT, recanalisatie of reperfusie. Ook was er geen verschil in de tijdsduur tussen begin van symptomen en de scans. Dit suggereert dat de tijdsduur voordat de patiënten in het ziekenhuis arriveren de meest bepalende factor is en het verder verkorten hiervan van groot belang is voor deze patiëntengroep.

In **hoofdstuk 8** is onderzocht of de nieuwe methode om permeabiliteit te bepalen kan helpen om bij binnenkomst te voorspellen welke patiënten zwelling gaan ontwikkelen. De resultaten laten zien dat de permeabiliteit een goede voorspeller is van hersenzwelling en dat deze de voorspelling met de CTA parameters bloedstolsel omvang en collateraal score verbetert. Dit suggereert dat de nieuwe methode om permeabiliteit te meten gebruikt kan worden ter evaluatie van patiënten bij binnenkomst en bij het beslissingsproces van behandeling bij patiënten die het risico hebben om zwelling te ontwikkelen.

## Conclusie

Dit proefschrift laat zien dat de Patlak methode alleen bij ernstige schade in staat is om de permeabiliteit van de bloed-hersen barrière te bepalen. Een nieuwe methode om permeabiliteit te bepalen kan zowel bloedingen als hersenzwelling voorspellen. Dit is alleen in het geval van hersenzwelling een aanvulling op al bekende voorspellers. Daarnaast blijkt een uitgebreide afsluiting van een van de grotere slagaders met slechte collateralen en daardoor een groter totaal ischemisch gebied met verhoogde permeabiliteit gerelateerd aan het optreden van hersenzwelling. Ook blijken recanalisatie en reperfusie sterk gerelateerd maar dat is niet in alle gevallen zo. Ten slotte is alleen een kleiner ischemisch gebied een onafhankelijke voorspeller van complete reperfusie.

# CHAPTER 10

Affiliations
List of publications
Dankwoord
Biography

# Affiliations


| | |
|---|---|
| Biessels, Geert Jan | Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht |
| Boiten, Jelis | Department of Neurology, Medical Center Haaglanden, The Hague |
| Bot, Joseph C.J. | Department of Radiology, VU University Medical Center, Amsterdam |
| Dankbaar, Jan Willem | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Dijk, Ewoud J. van | Department of Neurology, Radboud University Medical Center, Nijmegen |
| Dippel, Diederik W.J. | Department of Neurology, Erasmus MC University Medical Center, Rotterdam |
| Duijm, Lucien E.M. | Department of Radiology, Catharina Hospital, Eindhoven |
| Graaf, Yolanda van der | Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht |
| Hendrikse, Jeroen | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Hofmeijer, Jeannette | Department of Neurology, Rijnstate Hospital, Arnhem |
| Horsch, Alexander D. | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Kappelle, L. Jaap | Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht |
| Keizer, Koos | Department of Neurology, Catharina Hospital, Eindhoven |
| Kesselring, F. Oskar H.W. | Department of Radiology, Rijnstate Hospital, Arnhem |
| Kort, Paul L.M. de | Department of Neurology, St. Elisabeth Hospital, Tilburg |
| Lugt, Aad van der | Department of Radiology, Erasmus MC University |

| | |
|---|---|
| | Medical Center, Rotterdam |
| Luitse, Merel J.A. | Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht |
| Lycklama à Nijeholt, Geert J. | Department of Radiology, Medical Center Haaglanden, The Hague |
| Majoie, Charles B.L.M. | Department of Radiology, Academic Medical Center, Amsterdam |
| Mali, Willem P.T.M. | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Meijer, Frederick J.A. | Department of Radiology, Radboud University Medical Center, Nijmegen |
| Niesten, Joris M. | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Pleiter, C. Constantijn | Department of Radiology, St. Franciscus Hospital, Rotterdam |
| Rooij, Willem Jan van | Department of Radiology, St. Elisabeth Hospital, Tilburg |
| Roos, Yvo B.W.E.M. | Department of Neurology, Academic Medical Center, Amsterdam |
| Schaaf, Irene C. van der | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Schonewille, Wouter J. | Department of Neurology, St. Antonius Hospital, Nieuwegein |
| Seeters, Tom van | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Velthuis, Birgitta K. | Department of Radiology, University Medical Center Utrecht, Utrecht |
| Visser, Marieke C. | Department of Neurology, VU University Medical Center, Amsterdam |
| Vos, Jan Albert | Department of Radiology, St. Antonius Hospital, Nieuwegein |
| Walderveen, Marianne A.A. van | Department of Radiology, Leiden University Medical Center, Leiden |

| | |
|---|---|
| Wermer, Marieke J.H. | Department of Neurology, Leiden University Medical Center, Leiden |

## Dutch acute stroke study (DUST) investigators

| | |
|---|---|
| Academic Medical Center, Amsterdam | Majoie, Charles B.L.M.<br>Roos, Yvo B.W.E.M. |
| Catharina Hospital, Eindhoven | Duijm, Lucien E.M.<br>Keizer, Koos |
| Erasmus University Medical Center, Rotterdam | Lugt, Aad van der<br>Dippel, Diederik W.J. |
| Gelre Hospitals, Apeldoorn | Droogh-de Greve, Kitty E.<br>Bienfait, Henri Paul |
| Leiden University Medical Center, Leiden | Walderveen, Marianne A.A. van<br>Wermer, Marieke J.H. |
| Medical Center Haaglanden, The Hague | Lycklama à Nijeholt, Geert J.<br>Boiten, Jelis |
| Onze Lieve Vrouwe Gasthuis, Amsterdam | Duyndam, Debby A.<br>Kwa, Vincent I.H. |
| Radboud University Medical Center, Nijmegen | Meijer, Frederick J.A.<br>Dijk, Ewoud J. van |
| Rijnstate Hospital, Arnhem | Kesselring, F. Oskar H.W.<br>Hofmeijer, Jeannette |
| St. Antonius Hospital, Nieuwegein | Vos, Jan Albert<br>Schonewille, Wouter J. |
| St. Elisabeth Hospital, Tilburg | Rooij, Willem Jan van<br>Kort, Paul L.M. de |
| St. Franciscus Hospital, Rotterdam | Pleiter, C. Constantijn<br>Bakker, Stef L.M. |
| VU University Medical Center, Amsterdam | Bot, Joseph C.J.<br>Visser, Marieke C. |
| University Medical Center Utrecht, Utrecht | Velthuis, Birgitta K.<br>Schaaf, Irene C. van der<br>Dankbaar, Jan Willem |

Mali, Willem P.Th.M.
Seeters, Tom van
Horsch, Alexander D.
Niesten, Joris M.
Biessels, Geert Jan
Kappelle, L. Jaap
Luitse, Merel J.A.
Graaf, Yolanda van der

# CHAPTER 10

Affiliations
List of publications
Dankwoord
Biography

# List of publications

1. Bennink E, Stemerdink TA, **Horsch AD**, Velthuis BK, van der Schaaf IC, de Jong HWAM, Dankbaar JW. Thin slice CT perfusion improves small volume stroke detection. Manuscript

**2.** **Horsch AD**, Bennink E, van Seeters T, Kappelle LJ, van der Graaf Y, Mali WPThM, de Jong HWAM, Velthuis BK, Dankbaar JW, on behalf of the DUST investigators. Can blood-brain barrier CT perfusion derived permeability measurements predict hemorrhagic transformation in acute ischemic stroke? Manuscript

3. Dankbaar JW, Kerckhoffs KGP, **Horsch AD**, van der Schaaf IC, Kappelle LJ, Velthuis BK. Internal carotid artery stenosis and collateral recruitment in stroke patients. Submitted

**4.** **Horsch AD**, Velthuis BK, Bennink E, de Jong HWAM, Seeters T, Stemerdink TA, van der Worp HB, Kappelle LJ, Hofmeijer J, van der Graaf Y, Mali WPThM, Dankbaar JW, on behalf of the DUST investigators. Blood-brain barrier permeability measurements with CT-perfusion predict prominent edema in acute ischemic stroke. Submitted

5. Santos EM, Dankbaar JW, Treurniet KM, **Horsch AD**, Roos YB, Kappelle LJ, Niessen WJ, Majoie CB, Velthuis BK, Marquering HA; DUST Investigators. Permeable Thrombi Are Associated With Higher Intravenous Recombinant Tissue-Type Plasminogen Activator Treatment Success in Patients With Acute Ischemic Stroke. *Stroke*. 2016 Aug;47(8):2058-65

**6.** **Horsch AD**, Dankbaar JW, Stemerdink TA, Bennink E, van Seeters T, Kappelle LJ, Hofmeijer J, de Jong HW, van der Graaf Y, Velthuis BK; DUST investigators. Imaging Findings Associated with Space-Occupying Edema in Patients with Large Middle Cerebral Artery Infarcts. *AJNR Am J Neuroradiol.* 2016 May;37(5):831-7

7. van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, **Horsch AD**, Niesten JM, Luitse MJ, Majoie CB, Vos JA, Schonewille WJ, van Walderveen MA, Wermer MJ, Duijm LE, Keizer K, Bot JC, Visser MC, van der Lugt A, Dippel DW, Kesselring FO, Hofmeijer J, Lycklama À Nijeholt GJ, Boiten J, van Rooij WJ, de Kort PL, Roos YB, Meijer FJ, Pleiter CC, Mali WP, van der Graaf Y, Velthuis BK; Dutch acute stroke study (DUST) investigators. CT angiography and CT perfusion improve prediction of infarct volume in patients with anterior circulation stroke. *Neuroradiology.* 2016 Apr;58(4):327-37

8. van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, **Horsch AD**, Niesten JM, Luitse MJ, Majoie CB, Vos JA, Schonewille WJ, van Walderveen MA, Wermer MJ, Duijm LE, Keizer K, Bot JC, Visser MC, van der Lugt A, Dippel DW, Kesselring FO, Hofmeijer J, Lycklama À Nijeholt GJ, Boiten J, van Rooij WJ, de Kort PL, Roos YB, van Dijk EJ, Pleiter CC, Mali WP, van der Graaf Y, Velthuis BK; Dutch acute stroke study (DUST) investigators. The Prognostic Value of CT Angiography and CT Perfusion in Acute Ischemic Stroke. *Cerebrovasc Dis.* 2015;40(5-6):258-69

9. Geurts M, van der Worp HB, **Horsch AD**, Kappelle LJ, Biessels GJ, Velthuis BK; DUST investigators. No Relation between Body Temperature and Arterial Recanalization at Three Days in Patients with Acute Ischaemic Stroke. *PLoS One.* 2015 Oct 16;10(10):e0140777

10. Bennink E, Oosterbroek J, **Horsch AD**, Dankbaar JW, Velthuis BK, Viergever MA, de Jong HW. Influence of Thin Slice Reconstruction on CT Brain Perfusion Analysis. *PLoS One.* 2015 Sep 11;10(9):e0137766

**11. Horsch AD**, Dankbaar JW, van der Graaf Y, Niesten JM, van Seeters T, van der Schaaf IC, Kappelle LJ, Velthuis BK; DUST investigators. Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke. *Neuroradiology.* 2015 Dec;57(12):1219-25

12. Bennink E, **Horsch AD**, Dankbaar JW, Velthuis BK, Viergever MA, de Jong HW. CT perfusion analysis by nonlinear regression for predicting hemorrhagic transformation in ischemic stroke. *Med Phys.* 2015 Aug;42(8):4610-8

13. Smit EJ, Vonken EJ, Meijer FJ, Dankbaar JW, **Horsch AD**, van Ginneken B, Velthuis B, van der Schaaf I, Prokop M. Timing-Invariant CT Angiography Derived from CT Perfusion Imaging in Acute Stroke: A Diagnostic Performance Study. *AJNR Am J Neuroradiol.* 2015 Oct;36(10):1834-8

14. Luitse MJ, Dauwan M, van Seeters T, **Horsch AD**, Niesten JM, Kappelle LJ, Biessels GJ, Velthuis BK; Dutch acute stroke study (DUST). Acute nephropathy after contrast agent administration for computed tomography perfusion and computed tomography angiography in patients with acute ischemic stroke. *Int J Stroke.* 2015 Jun;10(4):E35-6

**15. Horsch AD**, Dankbaar JW, Niesten JM, van Seeters T, van der Schaaf IC, van der Graaf Y, Mali WP, Velthuis BK; Dutch Acute Stroke Study Investigators. Predictors of reperfusion in patients with acute ischemic stroke. *AJNR Am J Neuroradiol.* 2015 Jun;36(6):1056-62

16. Oosterbroek J, Bennink E, Dankbaar JW, **Horsch AD**, Viergever MA, Velthuis BK, de Jong HWAM. Predicting stroke outcome using DCE-CT measured blood velocity. *Medical Imaging* 2015: Proc. SPIE 9417

**17. Horsch AD**, Dankbaar JW, van Seeters T, Niesten JM, Luitse MJ, Vos PC, van der Schaaf IC, Biessels GJ, van der Graaf Y, Kappelle LJ, Mali WP, Velthuis BK. Relation between stroke severity, patient characteristics and CT-perfusion derived blood-brain barrier permeability measurements in acute ischemic stroke. *Clin Neuroradiol.* 2015 Feb 27

18. Van Seeters T, Biessels GJ, van der Schaaf IC, Dankbaar JW, **Horsch AD**, Luitse MJ, Niesten JM, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK; DUST investigators. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol. *BMC Neurol.* 2014 Feb 25;14:37

19. Niesten JM, van der Schaaf IC, van der Graaf Y, Kappelle LJ, Biessels GJ, **Horsch AD**, Dankbaar JW, Luitse MJ, van Seeters T, Smit EJ, Mali WP, Velthuis BK. Predictive value of thrombus attenuation on thin-slice non-contrast CT for persistent occlusion after intravenous thrombolysis. *Cerebrovasc Dis.* 2014;37(2):116-22

20. Niesten JM, van der Schaaf IC, Riordan AJ, de Jong HW, **Horsch AD**, Eijspaart D, Smit EJ, Mali WP, Velthuis BK. Radiation dose reduction in cerebral CT perfusion imaging using iterative reconstruction. *Eur Radiol.* 2014 Feb;24(2):484-93

21. Van Seeters T, Biessels GJ, Niesten JM, van der Schaaf IC, Dankbaar JW, **Horsch AD**, Mali WP, Kappelle LJ, van der Graaf Y, Velthuis BK; Dust Investigators. Reliability of visual assessment of non-contrast CT, CT angiography source images and CT perfusion in patients with suspected ischemic stroke. *PLoS One.* 2013 Oct 8;8(10):e75615

22. Bennink E, Riordan AJ, **Horsch AD**, Dankbaar JW, Velthuis BK, de Jong HW. A fast nonlinear regression method for estimating permeability in CT perfusion imaging. *J Cereb Blood Flow Metab.* 2013 Nov;33(11):1743-51

23. Niesten JM, van der Schaaf IC, Biessels GJ, van Otterloo AE, van Seeters T, **Horsch AD**, Luitse MJ, van der Graaf Y, Kappelle LJ, Mali WP, Velthuis BK; Dutch acute stroke trial (DUST).Relationship between thrombus attenuation and different stroke subtypes. *Neuroradiology.* 2013 Sep;55(9):1071-9

24. Luitse MJ, van Seeters T, **Horsch AD**, Kool HA, Velthuis BK, Kappelle LJ, Biessels GJ.Admission hyperglycaemia and cerebral perfusion deficits in acute ischaemic stroke. *Cerebrovasc Dis.* 2013;35(2):163-7

25. Smit E, Vonken EJ, Mendrik A, **Horsch AD**, Van der Schaaf IC, Dankbaar JW, Van Seeters T, Van Ginneken B, Prokop M. Timing-invariant reconstruction for deriving high-quality CT angiographic data from cerebral CT perfusion data. *Radiology.* 2012 Apr;263(1):216-25

26. Bruijnen RCG, Grimme FAB, **Horsch AD**, van Oostayen J, Zeebregts CJ, Reijnen, MM. Primary balloon expandable PTFE-covered stenting of focal infrarenal aortic occlusive disease. *J Vasc Surg.* 2012 Mar;55(3):674-8

**27. Horsch AD**, Van den Tillaart S, Tulner S. De duur van de competentiegerichte medisch specialistische vervolgopleiding kan niet korter. *Tijdschr Med Onderw.* Maart 2011; 30,1-2: 31-32

**28. Horsch AD**, van Oostayen J, Zeebregts CJ, Reijnen MM. The Rotarex and Aspirex mechanical thrombectomy devices. *Surg Technol Int.* 2009;18:185-92

29. Niekel MC, **Horsch AD**, v.d. Ven M, Reijnen MPPJ, Joosten FB. Right middle lobe torsion: evaluation with CT angiography. *Emerg. Radiol.* 2009 Sep;16(5):387-9

30. Macauley SL, **Horsch AD**, Oterdoom M, Zheng MH, Stewart GR. The effects of transforming growth factor beta2 on dopaminergic graft survival. *Cell Transplant.* 2004;13(3):245-52

# CHAPTER 10

Affiliations
List of publications
Dankwoord
Biography

# Dankwoord

Een proefschrift als dit is alleen mogelijk in samenwerking met een grote groep enthousiaste mensen; en ik ben daarom dankbaar voor alle grote en kleine bijdragen die ik over de afgelopen jaren gekregen heb. Een aantal personen wil ik graag in het bijzonder bedanken:

Allereerst wil ik alle patiënten en familieleden die hebben ingestemd aan het DUST onderzoek deel te nemen van harte bedanken. Hoewel u zelf geconfronteerd werd met de soms ernstige gevolgen van een herseninfarct was u desondanks bereid mee te werken aan een onderzoek waar u zelf geen baat bij zou hebben. Dat is zeer bewonderenswaardig en een voorbeeld voor velen.

Professor dr. W.P.Th.M. Mali, hartelijk bedankt voor de mogelijkheid die ik van u heb gekregen om onderzoek te doen op de afdeling Radiologie van het UMCU. Hoewel meestal meer op de achtergrond, was uw inbreng van groot belang. Ik hoop dat het uiteindelijk resultaat van dit proefschrift naar uw verwachting is.

Professor dr. Y. van der Graaf, Yolanda, ik heb jouw toegankelijke manier van werken zeer gewaardeerd. Vooral op het gebied van de keuze voor de juiste studieopzet en statistiek heb ik veel aan je te danken. Het geven van deskundige adviezen via Whatsapp in het weekend of 's avonds was geen probleem, en ook was je altijd geïnteresseerd in ontwikkelingen buiten het onderzoek.

Dr. B.K. Velthuis, Birgitta, de initiator en drijvende motor achter de DUST. Je bent onvermoeibaar en op bewonderingswaardige wijze in staat om tientallen ballen tegelijkertijd in de lucht te houden. Ik heb me meerdere malen afgevraagd of er ook momenten zijn waarop je niet werkt. Ook jij was zeer laagdrempelig benaderbaar en betrokken. Daarnaast wist je vaak extra suggesties te doen om de artikelen nog beter te maken. Mijn dank voor alle begeleiding die je mij gegeven hebt en ik wens je veel succes met je nieuwe functie.

Dr. J.W. Dankbaar, Jan Willem, ik denk dat het in het begin best lastig was om een promovendus te begeleiden die al wat langer meeloopt. Maar ik had geen betere directe begeleider kunnen hebben. Ik ben je zeer dankbaar voor de humorvolle begeleiding en pragmatische adviezen die ik al die jaren van jou gekregen heb. Ik hoop dat we in de toekomst nog vaker kunnen samenwerken.

De leden van de leescommissie, professor dr. J. Hendrikse, professor dr. J.H.J. Wokke, professor dr. A. Algra, professor dr. A. van der Lugt en Dr. M.J.H. Wermer, bedankt voor het lezen, beoordelen en goedkeuren van mijn proefschrift.

De overige leden van de DUST groep uit het UMC Utrecht. Met name professor dr. L.J. Kappelle, Jaap, en professor dr. G.J. Biessels, Geert Jan, ik wil jullie hartelijk bedanken voor alle inspanningen om de DUST tot een succes te maken en voor jullie waardevolle commentaar op mijn manuscripten. Daarnaast natuurlijk de overigen onderzoekers, Irene van der schaaf,

Jan Willem Dankbaar, Tom van Seeters, Joris Niesten, Merel Luitse en Marjolein Geurts, ik wil jullie bedanken voor jullie hulp bij de inclusies van patiënten, het vullen en controleren van de database, het beoordelen van de scans en het verbeteren van mijn manuscripten.

Professor dr. M.A.A.J. van den Bosch, Maurice, hartelijk dank voor je meedenken en interventie op het juiste moment. Ik denk dat dit proefschrift een bevestiging is van je goede beoordelingsvermogen.

DUST onderzoekers, neurologen en radiologen, laboranten, onderzoeksverpleegkundigen en assistenten in andere ziekenhuizen. Jullie wil ik hartelijk bedanken voor jullie enthousiasme voor het DUST onderzoek en het organiseren van de inclusies. Zonder jullie was dit onderzoek niet mogelijk en mijn waardering voor jullie bijdrage is groot.

Saskia van Amelsvoort, Anneke Hamersma en Cees Haaring van Trial bureau radiologie, bedankt voor de gezellige donderdagochtend besprekingen en de hulp bij het organiseren van de logistiek rond de CT-scans en de radiologische database. Voor het laatste wil ik ook Mireille Velthuis en Eva Hernandez bedanken, die als onbaatzuchtige vrijwilligsters een belangrijke rol hebben gespeeld bij het perfectioneren van deze data.

Ans de Ridder, Danielle Derks, Dorien Slabbers, Marrit van Buuren en Paut Greebe van het trial bureau neurologie, dank voor jullie bijdrage aan het klinische deel van de DUST-database.

Roy Sanders, Karin van Rijnbach, Chris van Kesteren, Jan de Groot van fotografie Radiologie. Hartelijk dank voor jullie hulp bij het maken van het drukwerk voor de DUST, zoals patiënten informatiefolders, stickers en kerstkaarten.

Stafsecretariaat Radiologie en met name Marja Kool. Jullie bereidheid om vaak op korte termijn allerlei zaken te willen regelen was erg prettig.

Rudy van der Lek, Martijn Klaver, Sven de Vilder, Kees van Kesteren van technisch cluster. Allen hartelijk dank voor jullie hulp als er weer eens een kabel of computer was die ‘nee’ zei. Rudy wil ik nog extra bedanken voor alle hulp rond het DUST werkstation en voor de laptop service op afstand.

Alle onderzoekers van de afdeling radiologie waarmee ik de afgelopen jaren koffie gedronken of geluncht heb. Een waarschijnlijk niet complete lijst: Alan, Alexander, Alexandra, Andor, Anja, Annemarie, Anouk, Arthur, Bartjan, Beatrijs, Bertine, Björn, Cécile, Charlotte, Dominika, Edwin, Esther, Ewoud, Floor, Gisela, Hamza, Hanke, Jaap, Jan Willem, Jesse, Jet, Jill, Jip, Joost, Joris, Laura, Liesbeth, Lisa, Maarten, Malou, Mandy, Marianne, Marlijne, Merel, Mies, Niek, Nikki, Nolan, Onno, Reinoud, Remko, Rianne, Ricardo, Richard, Suzanne, Tim, Thijs, Thomas, Wieke, Wilco, Wouter en Zacharias. Bedankt voor jullie interessante verhalen en collegialiteit.

Ewoud Smit, hartelijk dank voor je hulp bij allerhande zaken en leuke gesprekken. Je hebt

de goede eigenschap dat je altijd bereid bent om je omgeving te helpen en bent daarin een voorbeeld voor anderen. Ik hoop dat jij ook snel kan promoveren.

Edwin Bennink en Hugo de Jong, jullie wil ik met name bedanken voor het ontwikkelen van de NLR permeabiliteitssoftware en jullie waardevolle commentaar op mijn manuscripten.

Opleiders, de maatschap radiologie en assistenten van het Rijnstate Ziekenhuis Arnhem. Zonder jullie flexibiliteit om één dag per week mijn radiologisch werk te doen was dit proefschrift niet mogelijk geweest. Mijn hartelijke dank daarvoor.

Mijn kamergenoten Jan Willem Dankbaar, Tom van Seeters, Joris Niesten en Thijs Braber. Hoewel ik vaak maar 1 dag per week aanwezig was heb ik mij altijd deel gevoeld van de belevenissen van de 'DUST'-kamer op E2. Tijdens de borrels buiten het werk was duidelijk dat jullie niet alleen in de wetenschap excelleren.

Alle andere vrienden, kennissen en familieleden. Hartelijk dank voor jullie interesse in mijn persoon en de ontwikkelingen tijdens dit project. Hoewel niet altijd even direct duidelijk is jullie betrokkenheid van groot belang geweest.

Mijn paranimfen, Rutger Bruijnen en Ernesto Kerkhof, dank voor jullie vriendschap en paranimfische inspanningen.

Ze zeggen wel eens: 'you have to select your parents carefully', en dat is zeldzaam goed gelukt. Ik had me geen betere kunnen wensen! Dank voor jullie betrokkenheid en dat jullie mij altijd gestimuleerd hebben om nieuwe uitdagingen aan te gaan.

Alison, tá mo chroí lán toisc go bhfuil tú i mo shaol. Chomh díograsach is atá tù, do rannpháirtíocht neamh -choinníollach agus cumas maithiúnas a fhesicint i ngach éinne, chuireann siadsan íonadh an domhain orm! Gan dabht ar bith, Alison mo chroí, is tusa fior saibhris an domhain. Mo ghrá go deo thú.

# CHAPTER 10

Affiliations
List of publications
Dankwoord
Biography

The author was born on the 21st of June 1971 in Voorburg, The Netherlands. He passed his high school exams at the Gymnasium Haganum in The Hague, The Netherlands, in 1990 and studied Spanish and general life skills in Salamanca, Spain, for one year after this. He subsequently studied (marine) biology at the University of Groningen, and started medicine in 1995.

After finishing his medical training at the University of Groningen in January 2002, he initally pursuit a career in neurosurgery starting for one year at the VU Medical Center in Amsterdam, The Netherlands. He then lived for four years in the United Kingdom and did his surgical rotation in Southampton (neurosurgery), Coventry (trauma and orthopedics), Sunderland (general surgery and vascular surgery), Cambridge (neurosurgery and neuro-intensive care) and Leeds (neurosurgery). He obtained his membership of the royal college of surgeons (Edinburgh) in 2006.

In 2007 he changed his career to radiology and started his registrar training in Rijnstate hospital in Arnhem, The Netherlands, under supervision of Dr. Tj.G. Wiersma and Dr. F.B.M. Joosten. In his second year he started to work for one day a week with the Dutch acute stroke study (DUST) group (led by Dr. B.K. Velthuis), which finally resulted in this thesis. During his registrar training he also committed himself to the national organisation for doctors in training ('De Jonge Specialist') of which he became vice-president in 2010.

After finishing his radiology training in 2012 he did a two year interventional radiology fellowship at the University Medical Center in Utrecht, The Netherlands, under supervision of Prof. Dr. W.P.Th.M. Mali and Prof. Dr. M.A.A.J. van den Bosch. Since January 2015 he has been working as a consultant interventional and diagnostic radiologist in Bristol, United Kingdom.