Volumetric and spatial accuracy of CTP estimated ischemic core volume in patients with acute ischemic stroke

Jan W. Hoving[1,2], Henk A. Marquering PhD[2,3], Charles B.L.M. Majoie MD[2], Nawaf Yassi PhD[1,4], Gagan Sharma MCA[1], David S. Liebeskind MD[5], Aad van der Lugt MD[6], Yvo B. Roos MD[7], Wim van Zwam MD[8], Robert J. van Oostenbrugge MD[9], Mayank Goyal MD[10], Jeffrey L. Saver MD[11], Tudor G. Jovin MD[12], Gregory W. Albers MD[13], Antoni Davalos MD[14], Michael D. Hill MD[15], Andrew M. Demchuk MD[15], Serge Bracard MD[16], Francis Guillemin PhD[17], Keith W. Muir PhD[18], Philip White MD[19], Peter J. Mitchell MMed[20], Geoffrey A. Donnan MD[4], Stephen M. Davis MD[1], Bruce C.V. Campbell PhD[1]

1. Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Australia
2. Department of Radiology and Nuclear Medicine, Academic Medical Center, Amsterdam, the Netherlands
3. Department of Biomedical Engineering and Physics, Academic Medical Center, Amsterdam, the Netherlands
4. The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Australia
5. Neurovascular Imaging Research Core, Department of Neurology, University of California at Los Angeles, Los Angeles, California, USA
6. Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, the Netherlands
7. Department of Neurology, Academic Medical Center, Amsterdam, the Netherlands

8. Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute (CARIM), Maastricht, the Netherlands
9. Department of Neurology, University Medical Center (MUMC) and Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands
10. Department of Radiology, University of Calgary, Foothills Hospital, Calgary AB, Canada
11. Department of Neurology, University of California Los Angeles, Los Angeles, California, USA
12. Stroke Institute, Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh
13. Stanford Stroke Center, Stanford University, Stanford, California, USA
14. Department of Neuroscience, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Barcelona, Spain
15. Department of Clinical Neurosciences, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Foothills Hospital, Calgary AB, Canada
16. Department of Diagnostic and Interventional Neuroradiology, INSERM U 947, University of Lorraine and University Hospital of Nancy, Nancy, France
17. INSERM CIC-EC 1433 Clinical Epidemiology, University of Lorraine and University Hospital of Nancy, Nancy, France
18. Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow G51 4TF, Scotland, UK.
19. Institute of Neuroscience, Newcastle University and Dept. of Neuroradiology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
20. Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

Cover title: Accuracy of CTP estimated ischemic core volume

Keywords: ischemic stroke; stroke; endovascular treatment; computed tomography; magnetic resonance imaging

Word Count: 5128 (Abstract 271)

Corresponding Author:
A/Prof Bruce Campbell, Dept Neurology, Royal Melbourne Hospital, Parkville 3050, Australia
Tel: +61-3-9342-8448 Fax: +61-3-9342-8427
Email: bruce.campbell@mh.org.au

Abstract

Background and Purpose

The volume of estimated ischemic core using computed tomography perfusion (CTP) imaging can identify ischemic stroke patients who are likely to benefit from reperfusion, particularly beyond standard time windows. We assessed the accuracy of pre-treatment CTP estimated ischemic core in patients with successful endovascular reperfusion.

Methods

Patients from the HERMES and EXTEND-IA TNK databases who had pre-treatment CTP, >50% angiographic reperfusion, and follow-up MRI at 24h were included. Ischemic core volume on baseline CTP data was estimated using relative cerebral blood flow <30% (RAPID, iSchemaView). Follow-up diffusion MRI was registered to CTP and the diffusion lesion was outlined using a semi-automated algorithm. Volumetric and spatial agreement (using Dice similarity co-efficient, Average Hausdorff Distance and precision) were assessed and expert visual assessment of quality performed.

Results

In 120 patients, median CTP estimated ischemic core volume was 7.8(IQR 1.8-19.9)ml and median diffusion lesion volume at 24h was 30.8(IQR 14.9-67.6)ml. Median volumetric difference was 4.4(IQR 1.2-12.0)ml. Dice similarity coefficient was low (median 0.24, IQR 0.15-0.37). The median precision (positive predictive value) of 0.68(IQR 0.40-0.88) and Average Hausdorff Distance (median 3.1, IQR 1.8-5.7mm) indicated reasonable spatial agreement for regions estimated as ischemic core at baseline. Overestimation of total ischemic core volume by CTP was uncommon. Expert visual review revealed overestimation predominantly in white-matter regions.

Conclusion

CTP estimated ischemic core volumes were substantially smaller than follow-up DWI lesions at 24h despite endovascular reperfusion within 2h of imaging. This may be partly due to infarct growth. Volumetric CTP core overestimation was uncommon and not related to imaging-to-reperfusion time. Core overestimation in white-matter should be a focus of future efforts to improve CTP accuracy.

Introduction

Early reperfusion in acute ischemic stroke is the key to reducing disability.[1] Multiple randomized trials[2-8] have shown that endovascular thrombectomy reduces disability versus standard care within 6h of stroke onset. The DAWN[9] and DEFUSE3[10] trials have successfully used imaging selection based on CTP or MRI processed with RAPID software (iSchemaView, Mountain View, CA, USA) to identify patients >6h after last known well time who benefit from reperfusion. Although analyses of 0-6h data have not shown an interaction between CTP core volume and the treatment effect of endovascular thrombectomy, CTP may have diagnostic and prognostic value for patients within 6h.[11-13] Several studies assessing contemporaneous CTP and diffusion-weighted MRI (MR-DWI) have shown reasonable agreement in estimates of the extent of permanently injured tissue.[14,15] However, CTP results have varied between post-processing techniques and thresholds applied by different software.[11,16,17]

Although CTP is fast and easily accessible in the acute setting of ischemic stroke, it is recognized that cerebral blood flow (CBF) map segmentations tend to include false-positive regions in areas of hypodense white-matter (leukoaraiosis).[18] CBF is physiologically lower in white versus grey-matter and further reduced in regions of leukoaraiosis.[18] Given DAWN and DEFUSE3 results, standardized CTP post-processing software with validated thresholds is likely to be increasingly used clinically to select patients for reperfusion therapies beyond standard therapeutic time windows. A crucial question, therefore, is how reliable CTP estimates of irreversible injury are in the current endovascular paradigm of fast reperfusion.[19]

We aimed to assess the volumetric and spatial agreement of estimated ischemic core on CTP with follow-up infarct on DWI. We hypothesized that CTP data, when appropriately

thresholded, could provide a reliable volumetric and spatial estimation of the follow-up infarct.

Materials and methods

Patient selection

This study pooled individual patient data from seven randomized trials of endovascular thrombectomy (HERMES collaboration)[2-8,20,21] and from the EXTEND-IA TNK trial.[22] The EXTEND-IA TNK trial tested the safety and efficacy of intravenous tenecteplase versus alteplase prior to thrombectomy in ischemic stroke patients. The data that support the findings of this study are available from the corresponding author upon reasonable request. The degree of reperfusion post-thrombectomy was assessed on the final angiogram using the modified Treatment In Cerebral Infarction (mTICI) score. To best estimate the accuracy of baseline CTP after endovascular reperfusion, only patients who had substantial reperfusion (defined as mTICI 2b/3, i.e. reperfusion of >50% of the affected territory) were included in this analysis. Sensitivity analysis was performed in patients achieving mTICI 2c/3, i.e. reperfusion of all but a few distal cortical branches.[23] Patients were required to have technically adequate baseline CTP and 24h DWI follow-up. The following patient characteristics were noted: age, sex, baseline NIHSS, baseline estimated ischemic core volume, hypertension, atrial fibrillation, diabetes mellitus, blood glucose, and smoking. Ethics approval was obtained from the local institutional review boards and written informed consent was obtained from patients or legal representatives.

CTP post-processing

CTP data were post-processed using RAPID (v4.5, Research Mode) and visually checked for artefacts. Ischemic core was defined as relative CBF<30% of normal brain (see online supplement http://stroke.ahajournals.org).

Data co-registration and segmentation

The 24h follow-up DWI was coregistered to the baseline CTP. Hemorrhagic transformation (HT) was graded using the ECASS classification.[24] Sensitivity analysis was performed excluding patients with hemorrhagic infarction type 2 and parenchymal hematoma.

Assessment of volumetric and spatial agreement

The volumetric difference between CTP and DWI ischemic core was defined as DWI volume minus CTP core volume. Magnitude of volumetric difference is also reported. CTP and DWI lesion overlap was calculated using FSLMaths (see online supplement http://stroke.ahajournals.org) and spatial agreement assessed using FSLStats and the EvaluateSegmentation tool.[25] The Dice similarity coefficient was calculated to assess spatial agreement between CTP and DWI lesions. The positive predictive value (PPV) was used to assess the proportion of the initial CTP lesion that fell within the 24h diffusion lesion. Unlike Dice, PPV is not diminished by regions of infarction at 24h that fall outside the baseline CTP lesion, potentially reflecting infarct growth. We also used the Average Hausdorff Distance (AVD, the average of all minimum distances between the two segmentations) to quantify spatial agreement.[25] Patients with 0ml ischemic core within the CTP coverage were included in volumetric analyses but excluded from spatial analyses as the outcome measures were not calculable.

Regions of apparent CTP misclassification were visually assessed for topography (white versus grey-matter) and co-registration accuracy. The quantity of CTP lesion outside the follow-up infarct (defined as core volume overestimation) was quantitatively trichotomized as 0-5ml, 5-10ml and >10ml. To quantitatively assess the impact of co-registration inaccuracies

on the outcome metrics, we segmented the ventricles of 13 HERMES patients and 56 EXTEND-IA TNK patients (see online supplement http://stroke.ahajournals.org).

Statistical analysis

Statistical analysis was performed using SPSS (v24 IBM, Armonk, NY). Spearman Correlation Coefficient (ρ) was calculated for correlations between variables.

Results

One-hundred and twenty patients with baseline CTP and 24h MRI met inclusion criteria for this study. Follow-up imaging was performed at median 24.4h(IQR 22.0-27.8h). In HERMES, 523/738(71%) patients assigned to thrombectomy had substantial reperfusion,[7,8,21] and 61 had requisite imaging. On 20/March/2017, 130 stroke patients were included in the EXTEND-IA TNK trial, 76/130(58%) achieved substantial angiographic reperfusion and 59 had requisite imaging. Overall, 118/120(98%) patients were treated <6h after symptom onset. Only two HERMES patients had stroke onset-to-treatment time >6h (8.2 and 8.8h). Patient characteristics are detailed in Table 1.

Volumetric and spatial agreement analysis

For the 19/120(16%) patients without detectable ischemic core within the CTP coverage, the median follow-up infarct volume (and thus median volumetric difference between baseline CTP ischemic core and follow-up infarct volume) was 13.1(IQR 7.9-21.3)ml. In the remaining 101(84%) patients, the median estimated baseline ischemic core lesion volume of 7.8ml increased to 30.8ml on 24h DWI with a median difference of 25.4ml (Table 1). Overall, the median volumetric difference was 25.4(IQR 10.0-63.7)ml. In sensitivity analysis excluding patients with HT, the median volume difference was 20.9ml. Median volume

198 difference in the 20 patients with HT was 69.1(IQR 24.3-142.2)ml. Increased absolute
199 volumetric difference was associated with increased estimated baseline ischemic core volume
200 (ρ=0.36, p<0.0001, Figure 1).
201
202 The median Dice was 0.24(IQR 0.15-0.37). The median overlap of baseline and 24h lesions
203 was 4.4(IQR 1.2-12.0)ml. However, the median PPV was 0.68(IQR 0.40-0.88). The median
204 AVD was 3.1(IQR 1.8-5.7)mm. Data are summarized in Table 2 and results of sensitivity
205 analysis in patients with almost complete reperfusion were similar (supplementary Table I,
206 http://stroke.ahajournals.org). As a measure of the influence of registration accuracy on the
207 maximum achievable spatial agreement, manual segmentation of ventricles had median Dice
208 0.79(IQR 0.71-0.84), median PPV 0.81(0.72-0.87), and median AVD 0.4(0.2-0.6)mm.
209
210 *Ischemic core overestimation and expert visual qualitative assessment*
211 There were 6/120(5%) patients with CTP estimated ischemic core volume larger than the 24h
212 DWI lesion volume, median volumetric difference 4.5(range 0.6-18.9)ml. Visual analysis of
213 lesion spatial overlap indicated that 91/120(76%) patients had some region of baseline core
214 outside the 24h infarct. Apparent core overestimation was 0.1-5.0ml in 63/120(53%) patients
215 (median 1.1, IQR 0.3-3.1ml) and located in white-matter in 46/63 patients. There were 21/120
216 (18%) patients with 5-10ml core overestimation (median 6.9, IQR 5.9-8.1ml), located in
217 white-matter in 18/21 patients and 17/120(14%) patients had >10ml core overestimation
218 (median 18.3, IQR 14.3-25.5ml), 14/17 located predominantly in white-matter. Nine patients
219 (9%) showed regions of baseline ischemic core that were not included in the follow-up infarct
220 most likely due to poor registration, as judged by the same anatomical structures being
221 included in both lesions. While misregistration may also have contributed to ischemic core

overestimation in other patients, the overrepresentation of white-matter regions was substantial (Figure 2).

Effect of time from imaging to reperfusion

Median time between baseline imaging and reperfusion was 114(IQR 82-159) min. CTP spatial accuracy was not associated with imaging-to-reperfusion time using Dice (ρ=-0.08, p=0.41), AVD (ρ=0.08; p=0.43) or PPV (ρ=-0.02, p=0.84). Longer imaging-to-reperfusion time, however, was associated with an increased volumetric difference between baseline ischemic core and 24h follow-up infarct. (ρ=0.2, p=0.05, Figure 3). In spatial analysis, there was no significant difference in core overestimation between the 0-90min, 90-180min or >180min imaging-to-reperfusion time subgroups (Figure 4). The median core overestimation in spatial analysis was 2.2(IQR 0.6-7.4)ml for 0-90min, 2.9(IQR 0.6-6.8)ml for 90-180min, and 7.4(IQR 3.5-17.8)ml for >180min subgroups (p=0.03 for 0-90 vs. >180min and p=0.03 for 90-180 vs. >180min). The median volume difference was 25.4(IQR 6.0-35.7)ml for 0-90min, 22.8(IQR 11.2-51.3)ml for 90-180min, and 60.0(IQR 21.1-91.7)ml for >180min subgroups.

Discussion

This study comparing baseline estimated ischemic core using a CTP-CBF threshold <30% of normal brain has demonstrated moderate spatial and volumetric agreement with follow-up DWI lesion. Volumetric overestimation of the ischemic core was rare. A degree of false positive core segmentation was detected in 76% of patients using spatial analysis, but was >10ml in only 14% and co-registration inaccuracy may have also contributed. Most patients that showed quantitative core overestimation by CTP had false positive areas in white-matter

adjacent to the lesion. Interestingly, there was no evidence that spatial and volumetric accuracy was reduced in patients with shorter imaging-to-reperfusion time.

Some previous studies of CTP ischemic core segmentation accuracy have used contemporaneous diffusion MRI as the reference standard. CBF-based thresholds consistently outperformed cerebral blood volume based thresholds.[26-28] However, obtaining both CT and MRI before intervention is impractical in the current era of fast endovascular workflow. There is also potential for partial reversal of diffusion lesions with rapid reperfusion,[29] although reversal is uncommon when a sufficiently low apparent diffusion contrast threshold is used to define ischemic core.[30]

We have taken an alternative approach to CTP accuracy assessment and studied follow-up diffusion lesions in patients with early reperfusion. This has practical advantages, but its accuracy depends on the modality of imaging, the time between CTP and reperfusion (in which infarct growth can continue), and the completeness of reperfusion. Voxel-based subanalysis in the MR CLEAN database using Philips CTP analysis software (Philips Medical Systems BV, Best, The Netherlands) suggested that CTP misclassified a considerable amount of the ischemic core volume compared to follow-up infarct (median 34ml).[17] The different processing software and thresholds for infarction (based on cerebral blood volume) substantially differed from the processing pathway and relative CBF<30% threshold applied in RAPID. Large differences in CTP analysis results between software packages have been demonstrated previously.[31,32] In addition, ischemic core volumes were considerably larger in MR CLEAN than in our study (median 49.7ml vs. 7.8ml) and the difference in results supports our finding that increased baseline ischemic core volume is associated with increased volumetric difference compared to follow-up infarct volume. RAPID has been shown to more

accurately estimate the follow-up infarct volume than other imaging packages[33,34] and was used in SWIFT PRIME[5], EXTEND-IA[3], DAWN[9] and DEFUSE3[10]. A recent subanalysis of the SWIFT PRIME trial[35] using RAPID showed good volumetric accuracy in predicting the follow-up infarct in acute stroke patients. The median baseline ischemic core volume in that study was smaller than in our population (4 (IQR 0-13)ml versus 7.8 (IQR 2-19)ml, as was the median follow-up infarct volume (18.7 (IQR 8.9-48.9)ml versus 30.8 (IQR 14.9-75.2)ml. Predictably, these smaller infarcts led to smaller volumetric inaccuracies in SWIFT PRIME (14.8 [IQR 4.9-33.7]ml) than in our study (25.4 [IQR 10.0-63.7]ml).

Superficially, the spatial agreement of baseline CTP ischemic core and follow-up infarct with a Dice co-efficient of 24% appears poor. This might be partially explained by the limitations of co-registering different imaging modalities. Also, sensitivity analysis demonstrated greater inaccuracy in patients who developed HT and associated edema which also impacted the spatial agreement. However, the trend to increased volumetric difference with increasing imaging-to-reperfusion time supports a contribution of interval infarct growth. Infarct growth (which can occur despite endovascular reperfusion because of delay between imaging and reperfusion or incomplete reperfusion) lowers Dice but is unrelated to CTP core segmentation accuracy. When the potential effect of infarct growth is accounted for using the PPV, a median 68% of the baseline CTP ischemic core fell within the follow-up infarct. This should be viewed in the context of the 81% precision achieved when comparing ventricle segmentations, which provides an estimate of the best possible performance allowing for co-registration inaccuracies. Both contemporaneous DWI and follow-up infarct approaches involve registration of DWI to CT, which has inherent inaccuracies due to echoplanar image distortion and differing slice thicknesses.

In this study, the estimated ischemic core volume on baseline CTP was generally smaller than the infarct volume as shown on the 24h follow-up MRI scan. This contrasts with previous studies suggesting that CTP may overestimate the final infarction, leading to concerns about unwarranted exclusion of patients from reperfusion therapies.[19,36] Only 6 patients had smaller infarct volumes on 24h DWI than on baseline CTP.

There are several potential reasons for larger infarct volumes at 24h than were estimated at baseline. The rCBF threshold of <30% used was specifically selected to increase specificity at the cost of sensitivity.[37] A RAPID rCBF threshold of <38% improves volumetric agreement, but substantially overestimates core in some patients. Hence the 30% threshold was chosen to reduce the risk of unwarranted exclusion of patients from treatment. There was potential for interval infarct growth in the median 114 minutes between imaging and reperfusion. Notably, even the subgroup with <90min of imaging to reperfusion time generally had smaller CTP volumes compared to DWI follow-up lesion volumes. There was also potential for infarct growth in regions that remained hypoperfused as mTICI 2b only requires restoration of flow to >50% of the affected territory. However, patients with almost complete (mTICI 2c/3) reperfusion had very similar volumetric differences. Vasogenic edema also develops and, while not as pronounced at 24h as at 3-5 days, may inflate the measured infarct volume. We acknowledge that distinguishing the effect of interval infarct growth and edema from core underestimation by CTP is challenging.

In visual assessment of reasons for spatial inaccuracies, almost all the patients had estimated CTP core in white-matter regions that fell outside the follow-up infarct at 24h. While these only amounted to >10ml in 14% of patients, the accurate classification of tissue viability in white-matter should be a focus of future attempts to improve the accuracy of CTP ischemic

core segmentation. The challenges of quantitatively different CBF and tolerance of ischemic insult in grey and white-matter are well known and the presence of old established ischemic damage as well as leukoaraiosis exacerbates this with further reductions in CBF.[38] Robust automated grey/white segmentation on CT would be required to implement differential CBF thresholds based on tissue type into current processing pipelines, and this remains challenging.

A limitation of this analysis is the potential for infarct growth beyond 24h. It is known that ischemic core continues to evolve in the days after stroke onset, although true expansion into previously unaffected territory is less likely after substantial reperfusion, as was required in this study.[39] However, all time points for assessment have limitations. Later assessment at 5 days, e.g. in DEFUSE2[40], is at the of peak of edema and overestimates the true infarct volume. At 90 days there is atrophy which underestimates the true infarct volume. Our results apply to one specific CTP rCBF threshold processed with RAPID software and would differ with other thresholds and likely with other software.[31,32] Patients included in the HERMES and EXTEND-IA TNK database had relatively small ischemic core volumes at baseline, despite broad inclusion criteria in most of the contributing trials. MR CLEAN, ESCAPE, REVASCAT and EXTEND-IA TNK had no upper limit on core volume, EXTEND-IA allowed up to 70ml and SWIFT PRIME up to 50ml. The distribution of core volumes in this analysis was similar to that in DAWN and DEFUSE3 which supports the generalizability of our data. However, this analysis provides limited information on the accuracy of ischemic core volume prediction in patients with larger baseline ischemic core which may differ, based on the observed association between baseline infarct volume and volumetric discrepancy.

Conclusion

CTP estimated ischemic core volumes were substantially smaller than follow-up DWI infarct lesions at 24h, particularly in patients with longer imaging to reperfusion times. Despite effective endovascular reperfusion, this may have resulted, at least in part, from infarct growth between CTP and reperfusion or subsequent infarct growth because of incomplete reperfusion or HT. This presents a methodological challenge for ischemic core validation studies. Detailed analysis revealed core overestimation predominantly in white-matter regions that should be the target of future efforts to improve CTP ischemic core accuracy. Importantly, volumetric overestimation of ischemic core by CTP was rare. Contrary to previous literature, we did not find that shorter imaging-to-reperfusion time was associated with volumetric or spatial overestimation of core volume using CTP.

Sources of funding

None

Disclosures

CM has consulted for Stryker and the Dutch Heart Foundation (paid to institution). HM is founder and shareholder of Nico-lab. AvdL has consulted for Stryker and reports grants to his institution from Penumbra. WvZ has consulted for Stryker and Cerenovus (paid to institution). JS is an employee of the University of California that has patent rights on retrieval devices for stroke; has served as an unpaid site investigator in multicenter trials sponsored by Medtronic, Stryker, and Neuravi for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled; has consulted for Medtronic, Stryker, and Neuravi and has received stock options from Rapid Medical for services as a consultant. TJ has consulted for Stryker Neurovascular as PI for the DAWN

370 trial; has consulted for Fundacio Ictus as member of the Executive Committee RACECAT
371 trial; has served as advisor for Silk Road, Anaconda, Route92, FreeOX Biotech, and Blockade
372 Medical; has served in the Data Safety Monitoring Board of Cerenovus. PW has consulted for
373 Microvention and Stryker and his institution received a grant from Microvention. KM reports
374 grants to his institution for the PISTE trial from the Stroke Association, the NIHR Health
375 Technology Assessment programme, Medtronic and Codman. MG has a licensing agreement
376 with GE Healthcare for further development of systems of efficient stroke diagnosis. GA
377 reports research support from the NIH(U01NS092076, 1U10NS086487), equity interest in
378 iSchemaView and consulting fees from Medtronic and iSchemaView. AD has consulted for
379 Medtronic; reports a research grant by Medtronic; reports engagements as lecturer for
380 Medtronic. MH reports a research grant from Medtronic; reports stock ownership in Calgary
381 Scientific Inc. AD reports honoraria for CME events from Medtronic. PM reports unrestricted
382 grants to his institution from Medtronic, Stryker and Codman Johnson and Johnson, and has
383 consulted for Codman Johnson and Johnson, and Microvention. GD reports speaking
384 engagements with Boehringer Ingelheim. SD reports a research grant from NHMRC
385 Australia.
386

References

1. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al. Magnetic-resonance-imaging profiles predict clinical response to early reperfusion. *Ann neurol*. 2006;60:508-517
2. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *NEJM*. 2015;372:11-20
3. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *NEJM*. 2015;372:1009-1018
4. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *NEJM*. 2015;372:1019-1030
5. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *NEJM*. 2015;372:2285-2295
6. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8h after symptom onset in ischemic stroke. *NEJM*. 2015;372:2296-2306
7. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE). *Lancet Neurol*.15:1138-1147
8. Muir KW, Ford GA, Messow C-M, Ford I, Murray A, Clifton A, et al. Endovascular therapy for acute ischaemic stroke. *JNNP*. 2017;88:38-44.

9. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6-24h after stroke with a mismatch between deficit and infarct. *NEJM*. 2018;378:11-21

10. Albers GW, Lansberg MG, Kemp S, Tsai JP, Lavori P, Christensen S, et al. Thrombectomy for Stroke at 6-16h with Selection by Perfusion Imaging. *NEJM*. 2018;378:708-718.

11. Borst J, Berkhemer OA, Roos YB, van Bavel E, van Zwam WH, van Oostenbrugge RJ, et al. Value of CTP-based patient selection for intra-arterial acute ischemic stroke treatment. *Stroke*. 2015;46:3375-3382

12. Campbell BC, Weir L, Desmond PM, Tu HT, Hand PJ, Yan B, et al. CTP improves diagnostic accuracy and confidence in acute ischaemic stroke. *JNNP*. 2013;84:613-618.

13. Campbell BCV MC, Menon B, Bracard S, Hill MD, Muir K, et al. Prognostic and treatment impact of penumbral imaging in pooled analysis of randomized trials of endovascular stent thrombectomy. *ESJ*. 2017;2:6.

14. Wintermark M, Reichhart M, Thiran JP, Maeder P, Chalaron M, Schnyder P, et al. Prognostic accuracy of cerebral-blood-flow measurement by perfusion-CT. *Ann Neurol*. 2002;51:417-432

15. Campbell BCV, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Comparison of CTP and MRI perfusion-diffusion mismatch in ischemic stroke. *Stroke*. 2012;43:2648-2653

16. Fahmi F, Marquering HA, Streekstra GJ, Beenen LF, Janssen NN, Majoie CB, et al. Automatic detection of CTP datasets unsuitable for analysis due to head movement of acute ischemic stroke patients. *J Healthcare Engineering*. 2014;5:67-78

17. Geuskens RR, Borst J, Lucas M, Boers AM, Berkhemer OA, Roos YB, et al. Characteristics of misclassified CTP ischemic core in patients with acute ischemic stroke. *PLoS One*. 2015;10:e0141571

18. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures. *NeuroImage*. 2006;31:1116-1128

19. d'Esterre CD, Boesen ME, Ahn SH, Pordeli P, Najm M, Minhas P, et al. Time-dependent CTP thresholds for patients with acute ischemic stroke. *Stroke*. 2015;46:3390-3397

20. Kakuda W, Abo M. [intravenous administration of tPA beyond 3h of the onset of acute ischemic stroke -- MRI-based decision making]. *Brain Nerve*. 2008;60:1173-1180

21. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke. *Lancet*.387:1723-1731

22. Campbell BC, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Yan B, et al. Tenecteplase versus alteplase before endovascular thrombectomy. *IJS*. 2017:1747493017733935

23. Goyal M, Fargen KM, Turk AS, Mocco J, Liebeskind DS, Frei D, et al. 2c or not 2c: Defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *JNIS*. 2014;6:83-86

24. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, Von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*. 1995;274:1017-1025

460 25. Taha AA, Hanbury A. Metrics for evaluating 3D medical image segmentation. *BMC*
461 *Medical Imaging*. 2015;15:29
462 26. Kamalian S, Kamalian S, Konstas AA, Maas MB, Payabvash S, Pomerantz SR, et al.
463 CTP mean-transit-time maps optimally distinguish benign oligemia from true "at-risk"
464 ischemic penumbra, but thresholds vary by postprocessing technique. *AJNR*.
465 2012;33:545-549
466 27. Bivard A, Levi C, Spratt N, Parsons M. Perfusion-CT in acute stroke. *Radiology*.
467 2013;267:543-550
468 28. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al.
469 Cerebral-blood-flow is the optimal CT-perfusion parameter for assessing infarct core.
470 *Stroke*. 2011;42:3435-3440
471 29. Labeyrie MA, Turc G, Hess A, Hervo P, Mas JL, Meder JF, et al. Diffusion lesion
472 reversal after thrombolysis. *Stroke*. 2012;43:2986-2991
473 30. Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, et al.
474 Thrombolytic reversal of acute human cerebral ischemic injury shown by
475 diffusion/perfusion MRI. *Ann Neurol*. 2000;47:462-469
476 31. Kudo K, Sasaki M, Yamada K, Momoshima S, Utsunomiya H, Shirato H, et al.
477 Differences in CT-perfusion maps generated by different commercial software.
478 *Radiology*. 2010;254:200-209
479 32. Fahmi F, Marquering HA, Streekstra GJ, Beenen LFM, Velthuis BK, VanBavel E, et
480 al. Differences in CT-perfusion summary maps for patients with acute ischemic stroke
481 generated by 2 software packages. *AJNR*. 2012;33:2074-2080
482 33. Austein F, Riedel C, Kerby T, Meyne J, Binder A, Lindner T, et al. Comparison of
483 perfusion-CT software to predict the final infarct volume after thrombectomy. *Stroke*.
484 2016;47:2311-2317

34. Kudo K, Christensen S, Sasaki M, Ostergaard L, Shirato H, Ogasawara K, et al. Accuracy and reliability assessment of CT and MR-perfusion analysis software using a digital phantom. *Radiology*. 2013;267:201-211

35. Albers GW, Goyal M, Jahan R, Bonafe A, Diener HC, Levy EI, et al. Ischemic core and hypoperfusion volumes predict infarct size in SWIFT PRIME. *Ann neurol*. 2016;79:76-89

36. Boned S, Padroni M, Rubiera M, Tomasello A, Coscojuela P, Romero N, et al. Admission CT-perfusion may overestimate initial infarct core. *JNIS*. 2016

37. Cereda CW, Christensen S, Campbell BC, Mishra NK, Mlynash M, Levi C, et al. A benchmarking tool to evaluate CTP infarct core predictions against a DWI standard. *JCBFM*. 2016;36:1780-1789

38. Zijdenbos AP, Dawant BM, Margolin RA, Palmer AC. Morphometric analysis of white-matter-lesions in MRI. *IEEE trans medical imaging*. 1994;13:716-724

39. Lansberg MG, O'Brien MW, Tong DC, Moseley ME, Albers GW. Evolution of cerebral infarct volume assessed by diffusion-weighted MRI. *Arch Neurol*. 2001;58:613-617

40. Wheeler HM, Mlynash M, Inoue M, Tipirneni A, Liggins J, Zaharchuk G, et al. Early diffusion-weighted-imaging and perfusion-weighted-imaging lesion volumes forecast final infarct size in DEFUSE2. *Stroke*. 2013;44:681-685

Figure legends

Figure 1. Scatter-plots of (a) baseline core volume and 24h follow-up infarct volume (ρ=0.65) (b) baseline core volume and absolute volumetric difference (ρ=0.07).

Figure 2. An 89-year-old man with right M1 segment middle cerebral artery occlusion. A) Cerebral blood flow map with B) RAPID estimation of ischemic core. C) 24h diffusion MRI after successful endovascular reperfusion indicating that the basal ganglia core was correctly identified on CTP, but there was core overestimation in adjacent white-matter. D) FLAIR indicating leukoaraiosis.

Figure 3. Scatter-plot of the association between imaging-to-reperfusion time and volumetric difference (calculated as 24h follow-up infarct volume – baseline infarct volume).

Figure 4. Ischemic core overestimation (spatial analysis) by imaging-to-reperfusion time A) Scatter-plot. B) Boxplot for the 0-90min, 90-180min and >180min imaging-to-reperfusion time subgroups. C) Volumetric difference between baseline estimated ischemic core and follow-up infarct volume in three subgroups by imaging-to-reperfusion time. Negative volume differences on the Y-axis indicate 24h volumes higher than baseline estimated core volumes.

Tables

Table 1. Patient characteristics [N=120]

Mean age, yr(SD)	69.6(12.9)
Sex, n(%) male	59(49)
Median baseline NIHSS*(IQR)	16(14-21)
Hypertension, n(%)	82(69)
Atrial fibrillation, n(%)	43(36)
Diabetes mellitus, n(%)	16(13)
Median glucose blood level, mmol/l(IQR)	6.4(5.6-7.4)
Smoking history, n(%)	39(35)
Median baseline core volume, ml(IQR)	7.8(1.8-19.9)
Median 24h follow-up infarct volume, ml(IQR)	30.8(14.9-67.6)
Median volumetric difference, ml(IQR)	25.4(10.0-63.7)

*National Institutes of Health Stroke Scale

534 **Table 2. Procedural and outcome data**

Median onset-to-imaging time, min(IQR) [N=117]	109(71-152)
Median imaging-to-reperfusion time, min(IQR) [N=117]	114(82-159)
Median onset-to-reperfusion time, min(IQR) [N=117]	233(187-288)
Median Dice similarity coefficient(IQR) [N=101]	0.24(0.15-0.37)
Median Precision(IQR) [N=101]	0.68(0.40-0.88)
Median Average Hausdorff Distance, mm(IQR) [N=101]	3.1(1.8-5.7)

535