MASARYK UNIVERSITY

FACULTY OF MEDICINE

DIAGNOSTICS AND RECANALIZATION TREATMENT OF ISCHEMIC STROKE

HABILITATION THESIS

in Neurology

(Collection of previously published scholarly works)

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I hereby declare that I wrote this habilitation thesis on my own, using the relevant resources listed in the references.

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Acknowledgement

I would like to express my sincere gratitude to all my motivating mentors (associate prof. Bijoy K. Menon, prof. Michael D. Hill, prof. Andrew M. Demchuk, prof. Mayank Goyal and prof. Robert Mikulík), whom taught me the basics of clinical research, statistics and strokology.

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Abstract

Stroke is a leading cause of adult disability worldwide. Clinical trials studying the reperfusion therapies (intravenous thrombolysis and mechanical thrombectomy) in acute stroke are of proven benefit. Speed and accuracy of diagnosis and interpretation of neuroimaging is critical before the treatment is initiated.

This habilitation thesis is divided into four main sections. The first section summarizes briefly stroke epidemiology and pathophysiology. The second section is devoted to modern neuroimaging tools in acute ischemic stroke with a special emphasis put on the visual and automated detection of early ischemic changes on baseline neuroimaging and clinical utility of the multiphase CTA. The third section is devoted to endovascular treatment (mechanical thrombectomy) of acute ischemic stroke. Its first part focuses on comparisons of nationwide endovascular data from the Czech Republic with a meta-analysis HERMES (*Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials*). Its second part presents an observational multicenter study assessing the effectiveness and safety of endovascular treatment versus best medical management in patients with CTA detected large vessel occlusion in anterior circulation and mild neurological deficit using recent data from comprehensive datasets and propensity score matching. The last section contains full texts of original publications (annexes) related to the topic of this habilitation thesis.

Abstrakt

Cévní mozková příhoda (CMP) je celosvětově hlavní příčinou invalidity dospělých. Randomizované studie zkoumající reperfúzní terapii (intravenózní trombolýza a mechanická trombektomie) u akutní CMP prokázaly její jednoznačný přínos (benefit) na výsledný klinický stav. Rychlost a přesnost diagnostiky a interpretace neurozobrazování je rozhodující před zahájením rekanalizační léčby.

Tato habilitační práce je rozdělena do čtyř hlavních částí. První část stručně shrnuje epidemiologii a patofyziologii CMP. Druhá část je věnována moderním neurozobrazovacím nástrojům s důrazem na automatickou detekci časných ischemických změn na vstupním neurozobrazení a klinický význam multifázické CTA. Třetí část je věnována endovaskulární léčbě (mechanické trombektomii) CMP. Její první oddíl je zaměřen na srovnání národních EVT dat za ČR s meta-analýzou HERMES (*Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials*). Druhý oddíl představuje observační multicentrickou studii hodnotící účinnost a bezpečnost endovaskulární léčby ve srovnání se standardní léčbou u pacientů s prokázaným uzávěrem velké mozkové tepny v přední mozkové cirkulaci a s nízkým neurologickým deficitem za použití tzv. propensity score matching analýzy. Poslední část (přílohy) obsahuje plné texty originálních prací souvisejících s tématem habilitační práce.

Section 1 – General Overview

Stroke represents a major cause of disability and is the second leading cause of death worldwide with an incidence of about 17 million per year. Improvements in primary prevention and lifestyle changes have led to a decreased incidence of age-adjusted stroke. Nevertheless, the overall number of strokes cases has been increasing and is expected to accelerate over the coming decades because of the aging in the population. It is predicted that stroke will account for 6.2% of the total burden of illness in developed countries by 2020. Without major advances in prevention, acute management and treatment, as well as in post-stroke rehabilitation, the burden and cost of this disease will considerably increase. (1) (2) (3)

Pathophysiology of Ischemic Stroke

Acute occlusion of a cerebral artery or arteriole leads to an immediate decrease in arterial blood flow in a particular vascular territory. Large vessel occlusion (LVO) caused by larger clots are associated with more severe neurological deficits than occlusions of more distal and smaller arteries. Immediately after the occlusion, cerebrovascular and systemic compensatory mechanisms are activated: acute stress reaction, blood pressure increase, recruitment of collaterals, etc., in order to maintain the sufficient perfusion. Blood flow reduction may be partially compensated by cerebral collateral circulation at different levels, mostly at the level of leptomeningeal (pial) collaterals. If the blood flow is above 20 ml/100 g per min (40% of a normal flow), cerebrovascular autoregulatory mechanisms lead to increased oxygen extraction. Below this level of blood flow, the neurotransmission will cease, and neurologic symptoms will manifest in correlation to the affected brain areas. Neurons are able to survive for minutes, but if sufficient blood flow is not restored they die at an average of 1.9 million nerve cells per minute. (4) The processes of ischemic and apoptotic changes are dynamic and occur within the next few hours/days. If the vessel is not opened and brain perfusion is not restored, the failure of these compensatory mechanisms beside the critical decrease in arterial perfusion lead to hypoxia progressing into ischemia, neuronal death, and eventually developing infarct. (5) (6)

Larger infarcts are associated with more severe deficits and worse functional outcome, e.g. infarction in the whole middle cerebral artery (MCA) territory has a poor prognosis, with only

5% functional independence after the first year in comparison to the M2 territory infarction. The urgent priority in acute ischemic stroke treatment is to reopen the occluded artery or arteries (recanalization), because early recanalization improves the short-term and the long-term outcomes. (7) (8)

Section 2 – Detection of Early Ischemic Changes and Utility of Time-variant Multiphase CT Angiography Color Maps in Acute Anterior Circulation Stroke due to Large Vessel Occlusion

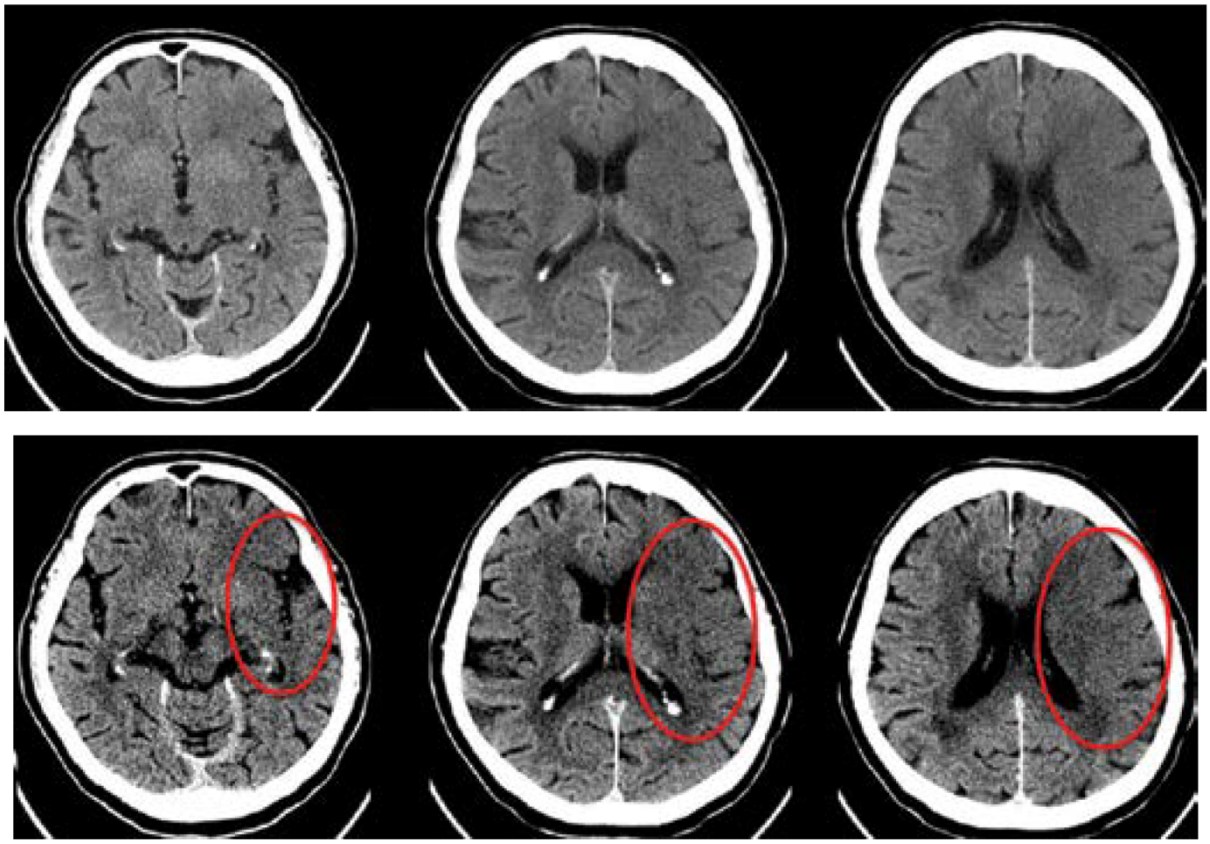
Acute ischemic stroke (AIS) due to LVO is a highly time-critical disease. In 2015, endovascular treatment (EVT) became the standard of care for LVO stroke patients presenting within 6 hours from symptom onset. (9) EVT represents a powerful treatment, but its effect is time-dependent. The overarching goal when performing EVT is therefore to treat the patient as fast as possible; however, not all patients will benefit from EVT, and screening the eligible patients is crucial in the selection process, in order not to cause harm. (10)

Currently, patients' selection is based on two main pillars: clinical characteristics (e.g. severity of neurological deficit, premorbid functional status, time of symptom onset) and brain imaging. Brain computed tomography (CT) is the most widely used and widespread modality for stroke imaging; non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP) represent important imaging tools, complementary to clinical examination and patient's history, aiding in the diagnosis and the decision-making of the subsequent therapy.

Assessment of Early Ischemic Changes

Early ischemic changes tend to develop in the first hours after stroke symptoms onset. In order to improve the rater detection of early ischemic changes on baseline NCCT, it is important to set up the so-called hard brain window. It assists the rater in differentiation of subtle changes in the grey and white matter density (window width [WW] 35 to 40 Hounsfield units [HU], window level [WL] 35-40 HU versus standard brain window WW 80 HU, WL 40 HU), **Figure 1**.

Figure 1: Comparison of the standard brain window and "hard brain" window



Legend: upper row (WW 80, WL 40), lower row = hard brain window (WW 40, WL 40) for proper assessment of early ischemic changes (marked with red ovals).

ASPECT Score

The most clinically used and validated score for assessing the extent of early ischemic changes in the anterior circulation is the Alberta Stroke Program Early CT Score (ASPECTS). The MCA territory is divided into 10 regions. For each region affected by early ischemic changes, one point is subtracted from a total score of 10 including the following areas: (A) at basal ganglia level [caudate (C), lentiform (L), internal capsule (IC), insula (I) and M1 to M3 territory]; (B) the M4 to M6 cortical regions at the supraganglional level. The ASPECTS is used as an imaging selection tool for EVT and it was proven to be a significant predictor of functional outcome. (11) (12) (13) On the one hand, it represents a validated grading system, and on the other and, the inter-rater reliability is limited. There is a trend to work on developing reliable and accurate software tools to help stroke physicians with the scan assessment and decision making.

Automated Imaging Tools for ASPECT Scoring

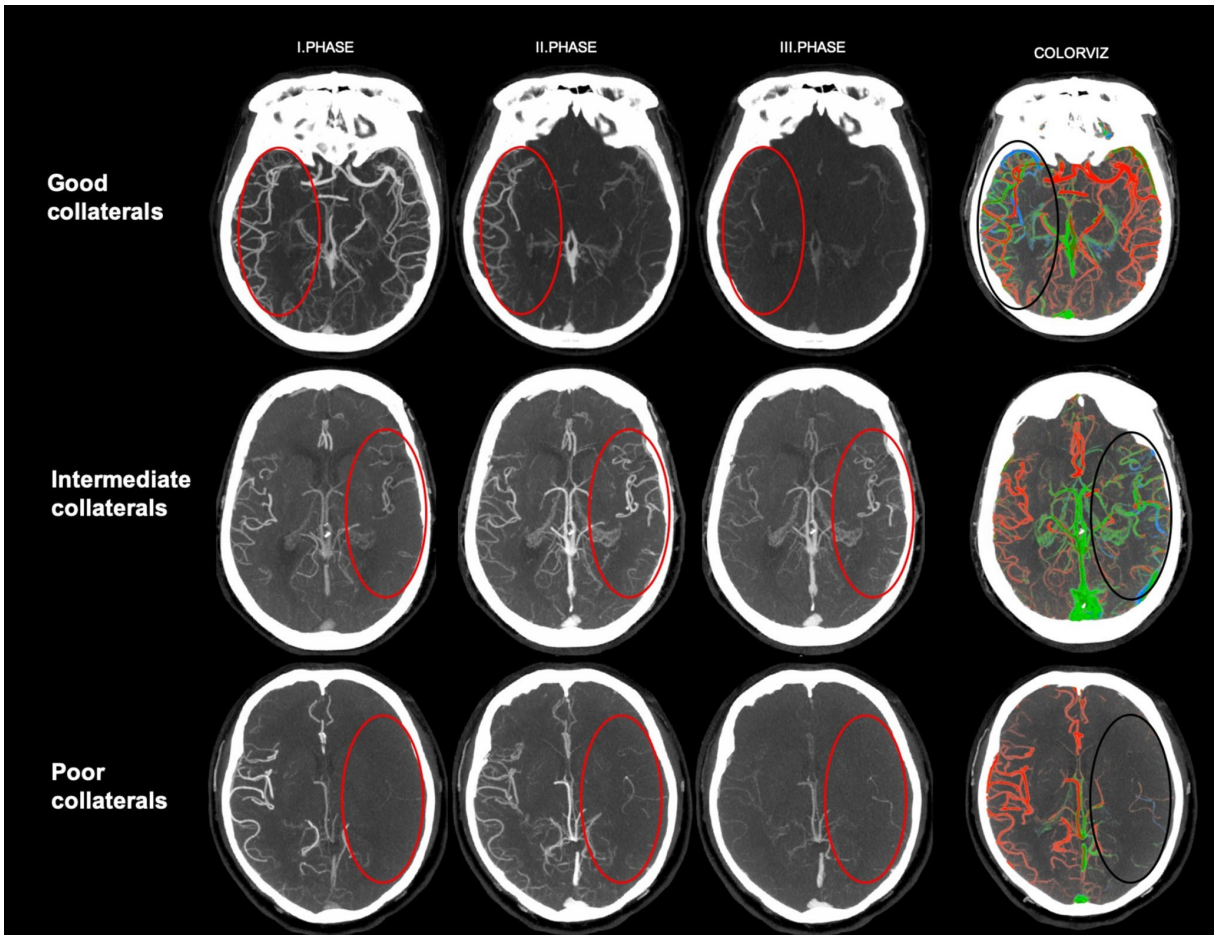
Neuroimaging interpretation in acute stroke requires some level of expertise, hence it might cause some time delays among less-experienced physicians (stroke clinician needs simple, quick and accurate imaging tools). The e-ASPECTS software (Brainomix, Oxford, U.K.) is a fully-automated ASPECT scoring tool for NCCT, which has previously demonstrated a scoring at an expert level. The advantage of e-ASPECTS is its potential to eliminate the inter-rater variability. Automated post-processing with RAPID software was used as an accurate prediction tool for irreversibly damaged tissue (infarct core), and tissue at risk of infarction (penumbra).
Section 2.1 is devoted to this subject in detail. The main aim was to compare the assessment of early ischemic changes by the expert reading and by the available automated software for NCCT and CTP and ultimately demonstrate the accuracy for the final infarct prediction.

Multiphase CTA and CTP in Determination of Irreversibly Damaged Brain Tissue (Core)

Baseline neuroimaging is also used to determine how much of brain tissue is already irreversibly damaged, since in patients with extensive early ischemic changes, tissue is unlikely to be salvaged by EVT, and the risk of reperfusion injury (futile recanalization) is higher. There are multiple ways of identifying irreversibly damaged tissue. The most commonly used imaging techniques are CTP and multiphase CTA (mCTA). Both techniques have been successfully used for EVT patient selection in randomized controlled trials, and both have their advantages and disadvantages: CTP maps can be quickly and easily interpreted even with limited imaging experience, because the color-coded display format is a clear visual indicator of pathology. (2) (14) (15) (16) On the other hand, CTP is susceptible to patient motion and post-processing artifacts and generating post-processed maps takes some time. mCTA is more robust against patient motion and requires less contrast and radiation dose. It is equally as reliable as CTP as an EVT selection and outcome prediction tool, and because it can easily be implemented without any additional technical requirements, it is particularly attracts smaller hospitals and places in which it is not possible to afford additional hardware and/or software. (17) However, the standard display format for mCTA consists of 3 separate gray scale images of the cerebral vessels (**Figure 2**), and evaluating the collaterals requires the reader to assess all three of them simultaneously. Our research team have recently described a new color-coded mCTA display format, in which all 3 mCTA series are consolidated in a single color-coded map, thereby potentially facilitating

and improving mCTA interpretation, (**Figure 2**) and (**ANNEX 1** and **ANNEX 2)**. mCTA color-maps therefore constitute a good alternative to facilitate interpretation of collateral status until fully automated collateral assessment becomes routinely available, particularly for less-experienced readers. Section 2.2 is devoted to this subject in detail.

Figure 2: Conventional and color-based collateral scoring



Legend: Top row – good collaterals. Most collaterals are opacified on the first mCTA phase and appear red on the color-map, which is consistent with a zero-phase delay. The vessel extent is nearly identical to the contralateral side. Middle row: intermediate collaterals. Most collaterals are opacified on the second mCTA phase and appear green on the color-map, which is consistent with a one-phase delay. The vessel extent is slightly reduced compared to the contralateral side. Bottom row: poor collaterals. The few visible collaterals are mostly opacified on the third mCTA phase and appear blue on the color-map, which is consistent with a two-phase delay. The vessel extent is markedly reduced compared to the contralateral side.

Imaging Paradigms and Randomized Controlled Trials

The vanguard trials that established efficacy of EVT in patients with AIS used various imaging criteria for patient selection. These ranged from simple paradigms like NCCT and single-phase CTA in the MR CLEAN and the RESILIENT trial, collateral imaging using mCTA in the ESCAPE trial and to multimodal MRI protocol in the THRACE trial. CTP was used exclusively in the EXTEND IA trial, a mixture of advanced imaging was used in the SWIFT PRIME trial (some mCTA and some CTP) and the late window DAWN and DEFUSE-3 trials had NCCT and CTP paradigms.

Each approach has its advantages and its drawbacks but the lack of standardization of imaging paradigms globally results in some misunderstanding about what types of patients are actually being enrolled into the studies. This makes comparison of patient populations and treatment effects difficult, but it also constitutes an opportunity to compare different imaging paradigms and try to find an optimal imaging approach; one that provides just enough information for treatment decision-making and outcome prediction, without delaying or compromising treatment by either obtaining unnecessary information or excluding patients whom may have benefited from treatment. Of all the imaging paradigms in use in patients with acute stroke, NCCT with single phase CTA is the simplest and arguably the fastest, but reliability of assessment of the extent of early ischemic changes is low, particularly among less-experienced physicians. Pial collateral status assessment has high specificity if the collaterals are good on a single-phase CTA but poor collateral filling could be a false result due to delay in timing of the contrast bolus with consequent arterial filling. Both CTP and mCTA provide time-resolved images that try to address the issue of mistimed bolus contrast influencing assessment of contrast enhanced CT in patients with acute stroke. In CTP, the brain is continuously scanned over 45 – 90 seconds, while in mCTA, three scans cycles are performed over 16-20 seconds. Due to its higher temporal resolution, the information content in CTP images is higher when compared to mCTA, but this comes at the cost of lower spatial resolution, higher motion susceptibility and requirement for algorithm based image postprocessing.

Section 2.1 Detection of ischemic changes on baseline multimodal computed tomography: expert reading vs. Brainomix and RAPID software

Based upon: CIMFLOVA, Petra, ***Ondrej VOLNY*(joint first author)****, Robert MIKULIK, Bohdan TYSHCHENKO, Silvie BELASKOVA, Jan VINKLAREK, Vladimir CERVENAK, Tomas KRIVKA, Jiri VANICEK a Antonin KRAJINA. Detection of ischemic changes on baseline multimodal computed tomography: expert reading vs. Brainomix and RAPID software. *Journal of Stroke & Cerebrovascular Diseases* [online]. 2020, **29**(9), 104978. ISSN 1052-3057.

Abstract

Background – The aim of the study was to compare the assessment of early ischemic changes by expert reading and available automated software for NCCT and CTP on baseline multimodal imaging and demonstrate the accuracy for the final infarct prediction.

Methods – Early ischemic changes were measured by ASPECTS on the baseline neuroimaging of consecutive patients with anterior circulation ischemic stroke. The presence of early ischemic changes was assessed a) on NCCT by two experienced raters, b) on NCCT by e-ASPECTS, and c) visually on derived CT perfusion maps (CBF<30%, Tmax>10s). Accuracy was calculated by comparing presence of final ischemic changes on 24-hour follow-up for each ASPECTS region and expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The sub-analysis for patients with successful recanalization was conducted.

Results – Of 263 patients, 81 fulfilled inclusion criteria. Median baseline ASPECTS was 9 for all tested modalities. Accuracy was 0.76 for e-ASPECTS, 0.79 for consensus, 0.82 for CBF<30%, 0.80 for Tmax>10s. e-ASPECTS, consensus, CBF<30%, and Tmax>10s had sensitivity 0.41, 0.46, 0.49, 0.57, respectively; specificity 0.91, 0.93, 0.95, 0.91, respectively; PPV 0.66, 0.75, 0.82, 0.73, respectively; NPV 0.78, 0.80, 0.82, 0.83, respectively. Results did not differ in patients with and without successful recanalization.

Conclusion – This study demonstrated high accuracy for the assessment of ischemic changes by different CT modalities with the best accuracy for CBF<30% and Tmax>10s. The use of automated software has a potential to improve the detection of early ischemic changes.

Introduction

The ASPECTS quantifies the extent of early ischemic changes in the MCA territory on baseline NCCT scans. (18) It has been proven to be a significant predictor of clinical outcome in patients with AIS in the anterior circulation. (12) (13) It is also used to select patients for EVT. (11) It represents a validated grading system, but the inter-rater variability has been questioned. Even experienced clinicians show only a 39% agreement in the identification of ischemic changes on NCCT involving more than one-third of the MCA territory. (19) Hence, there is a trend to develop reliable software tools to help stroke physicians in acute scan reading and subsequent decision making. (10) (16)

The e-ASPECTS software (Brainomix, Oxford, UK) is a fully-automated ASPECT scoring tool for NCCT, which has previously demonstrated a scoring on expert level. The advantage of e-ASPECTS is its potential to eliminate the inter-rater variability. (20) (21) (22) CTP has a potential to discriminate between irreversibly damaged tissue, infarct core, and tissue at risk of infarction, penumbra. (23) (24) It has been demonstrated that visual applying of ASPECTS into CTP parametric maps has a strong correlation with good clinical outcome (defined as modified Rankin scale [mRS] 0-2), with a prognostic value greater than NCCT ASPECTS. (25) (26) (27) (28) All previous studies have shown the highest correlation of good clinical outcome with cerebral blood volume (CBV) ASPECTS.

The most accurate prediction of irreversibly ischemic changes by automatic software post-processing with RAPID was shown for relative cerebral blood flow (CBF) less than 30% in comparison to the mean CBF of normally perfused brain parenchyma. (29) (30) This threshold was used in the randomized controlled trials with patient selection based on perfusion mismatch (SWIFT-PRIME, EXTEND-AI, DAWN, DEFUSE III) to define ischemic core. (31) (15) (32) (14) Severe hypoperfusion has been associated with irreversible necrosis of the ischemic lesion even after reperfusion. (33) In the DEFUSE and EPITHET meta-analysis, large regions of severe delay (>10 s) have been associated with poor outcome after reperfusion. (34) This finding suggests that higher Tmax may identify tissue with more severely reduced cerebral blood flow, which may have a substantial impact on the evolution of the acute ischemic lesion.

The main aim of our study was to evaluate how accurate the different CT modalities with and without software processing (consensus reading, e-ASPECTS, CBF<30%, Tmax>10s) assess early ischemic changes at baseline and what is their accuracy for final ischemia prediction.

Methods

Patient selection

Ethical approval was obtained from the local Institutional Review Boards (the Boards waived the need for patient consent). All patients with symptoms of AIS and no history of contrast allergy routinely underwent NCCT, mCTA from the aortic arch to the vertex and CTP in our institution.(17) If the diagnosis of AIS was confirmed by this neuroimaging protocol, NCCT was repeated within 24-32 hours to determine the extent and location of ischemia and diagnose potential complications such as hemorrhagic transformation. Radiological data of consecutive patients from March 2017 to September 2017 presenting with symptoms of AIS in the anterior circulation within 6 hours of last seen normal (symptom onset) were retrospectively reviewed. This time period was chosen in order to compare the reliability of the detection of early ischemic changes while the software for automatic detection of early ischemic changes was implemented into our institutional system. Inclusion criteria were: 1) availability of baseline NCCT with automatic software analysis, baseline CTP and follow-up 24-hour NCCT. Exclusion criteria were: 1) evidence of any intracranial hemorrhage or non-ischemic lesion, 2) negative findings on baseline diagnostic imaging and no ischemic changes on follow-up CT. We defined patients with successful reperfusion/recanalization angiografically as Thrombolysis in Cerebral Infarction (TICI) 2b-3 in patients treated with EVT or as >40% decrease in the 24-hour NIHSS score in patients treated with intravenous thrombolysis (IVT) only. (35) Sub-analysis of this subgroup was conducted.

Imaging Protocol

The imaging protocol set up in our stroke center combines NCCT, mCTA and CTP and both software programs were available during the study period for automatic analysis (Brainomix for NCCT and RAPID for CTP). NCCT was acquired on a multi-detector scanner (120kV, 328 mAs (419mAs/slice), Brilliance iCT 256; Philips Healthcare, Cleveland, OH) with a section thickness of 0.9mm and an image reconstruction of 3mm. For the CTP protocol,

40 ml of contrast agent (Iomeron 300; Mallinckrodt Pharmaceuticals; Dublin, Ireland) was power injected at 5 ml/s followed by a saline chase of 50 ml at 5 ml/s. Sections of 8cm thickness were acquired at 10 mm slice thickness. Scanning began after a delay of 5s from contrast injection in every 1.8s for 75s. After 24 hours, a NCCT was acquired for final infarct delineation in all patients.

Image Processing

NCCT scans were automatically analysed by the e-ASPECTS software (version 6.0, Brainomix, Oxford, UK). The e-ASPECTS software is a standardized, fully-automated, CE mark-approved ASPECTS scoring tool for NCCT, which has previously demonstrated scoring on an expert level. The e-ASPECTS software is based on a combination of advanced image-processing and machine-learning algorithms. Its scoring module operates on the standardized 3D images, classifying signs of ischemic damage and assigning them to ASPECTS regions. CT perfusion studies were post-processed using the RAPID software (iSchemaView, Menlo Park, CA, USA) to generate perfusion maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to the maximum of the residue function (Tmax). The RAPID software also automatically segmented and calculated volumes of the ischemic core (relative regional CBF<30%) and the critically hypoperfused tissue (Tmax>6s). (29)

Image review

Early ischemic changes were assessed on baseline NCCT by two experienced readers (a consultant neuroradiologist, PC, and a stroke neurologist, OV)* using the ASPECTS score defined by Barber et al. previously, blind to the results of the e-ASPECTS analysis, as well as to other baseline imaging modalities and follow-up NCCT. (13) Automatic segmentations of ASPECTS regions on e-ASPECTS derived scans were visually checked to avoid any severe inaccuracy. Otherwise, the given e-ASPECTS score were not modified and the original e-ASPECTS was noted. CTP maps were superposed on the CT-ASPECTS template and visually assessed by an experienced reader (PC). Ischemic changes on CTP maps were evaluated using the ASPECTS as follows: 1) on the CBF map as the area with CBF<30 % when compared to the contralateral hemisphere and 2) on the Tmax map as the area with Tmax>10s delay in the maximum contrast filling within the region of interest when compared to the contralateral hemisphere (**Figure 3**). The reader

was blind to findings on NCCT, perfusion baseline scans available in the summary of RAPID analysis were visually controlled to exclude any false positive CTP findings (e.g. chronic infarction). The final infarction was assessed on a 24-hour follow-up NCCT with consensus of the two readers (PC, OV), during a different session, one month after the previous assessment of the early ischemic changes on baseline NCCT. To support the reliability of the consensus reading, two radiologists (VC, TK) evaluated ASPECTS of 40 random admission NCCT and 40 follow-up scans (of different patients). The inter-rater agreement with the consensus was counted using weighted kappa (κ_w) and Krippendorf's alfa (α). The moderate agreement between raters was demonstrated for baseline NCCT (κ_w=0.53-0.54; α=0.72) and good to excellent agreement for follow-up imaging (κ_w=0.78-0.88; α=0.94)**. *PC and OV have 6-year experience with stroke imaging evaluation, 5-year experience in comprehensive stroke centre and both were trained in ASPECTS reading as members of the Calgary Stroke Program.

Statistical Analysis

Clinical and imaging baseline characteristics were summarized using descriptive statistics. The accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for particular ASPECTS regions (81 patients x 10 ASPECTS regions) at baseline imaging (e-ASPECTS, expert consensus reading, CBF<30%, Tmax>10s) in comparison with ASPECTS regions at the follow-up CT. The Bland-Altman plots were calculated to compare the differences between each baseline imaging method and follow-up ASPECTS. The sensitivity analysis of pooled data for the group with determined successful reperfusion/recanalization was conducted; clinical and imaging baseline characteristics were summarized using descriptive statistics and compared to the group with non-determined recanalization/reperfusion using Wilcoxon rank sum test; the accuracy, sensitivity, specificity, PPV, NPV as well as Bland-Altman plots were calculated. To compare the two subgroups, we calculated residuals between follow-up ASPECTS and each baseline ASPECT score method (e-ASPECTS, expert consensus reading, CBF<30%, Tmax>10) and analysed these residuals using Wilcoxon rank sum test. This study provides hierarchically structured data with 3 levels: subject ID, imaging modalities (e-ASPECTS, expert consensus reading, CBF<30%, Tmax>10s, and follow-up ASPECTS); and ASPECTS regions (M1-M6, Insula, Lentiform, Capsula, Caudate). We regarded regions as a fixed effect. The generalized estimating equation accommodating

clustering at the subject ID level was used (PROC GENMOD; SAS Institute Inc, Cary, NC). LS-means estimates of fixed effect "region" computed from generalized mixed model were graphically illustrated. All analyses were performed in Stata 16.1 (StataCorp LLC, College Station, TX, USA) and SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline scans of 263 patients were retrospectively reviewed; 16 patients with intracranial hemorrhage and 166 patients with either negative findings on all imaging modalities or missing follow-up imaging were excluded. Overall, 81 patients met all the criteria and were included into the analysis. Mean age was 70 years (standard deviation [SD] 14 years, range 30-92 years), 38 (46,9%) were women. Median baseline NIHSS was 9 (interquartile range [IQR]=4–17). The median time interval from symptom onset to CT was 156 mins (IQR=71-220); there were 12 patients with the unknow time of symptom onset or wake-up stroke. Median baseline ASPECTS was 9 for all tested modalities (IQR=8-10 for e-ASPECTS, IQR=7-10 for consensus, IQR=7-10 for CBF<30%, IQR 6-10 for Tmax>10s, median ASPECTS on follow-up NCCT was 8, IQR=5-9), left hemisphere was affected in 44 cases (54.3%). Fifty patients received intravenous thrombolysis and 19 patients had mechanical thrombectomy. Reperfusion was achieved in 11 patients in the mechanical thrombectomy group and in 22 patients in the IVT group, the data from mechanical thrombectomy and intravenous thrombolysis groups were pooled for further analysis (as determined recanalization).

Accuracy of baseline ASPECTS and follow-up ASPECTS was 0.76 for e-ASPECTS, 0.79 for expert consensus, 0.81 for CBF<30% and 0.8 for Tmax>10s. Sensitivity and specificity were 0.41 and 0.91 for e-ASPECTS; 0.46 and 0.93 for expert consensus; 0.49 and 0.95 for CBF<30%; 0.57 and 0.91 for Tmax>10s respectively. PPV and NPV were 0.66 and 0.78 for e-ASPECTS; 0.75 and 0.8 for expert consensus; 0.82 and 0.81 for CBF<30%; 0.73 and 0.83 for Tmax>10s, respectively, **Figure 4** and **Table 1**. Bland-Altman plots comparing differences in scores of baseline ASPECTS and follow-up ASPECTS are demonstrated in **Figure 5**. The mean difference between e-ASPECTS and follow-up was -1.16 ± 2.52 (median undercall of ASPECTS was -1), expert consensus and follow-up -1.16 ± 2.23 (median undercall was -1), CBF<30% and follow-up -1.15 ± 1.77 % (median undercall was -1), and Tmax>10s and follow-up -0.59 ±

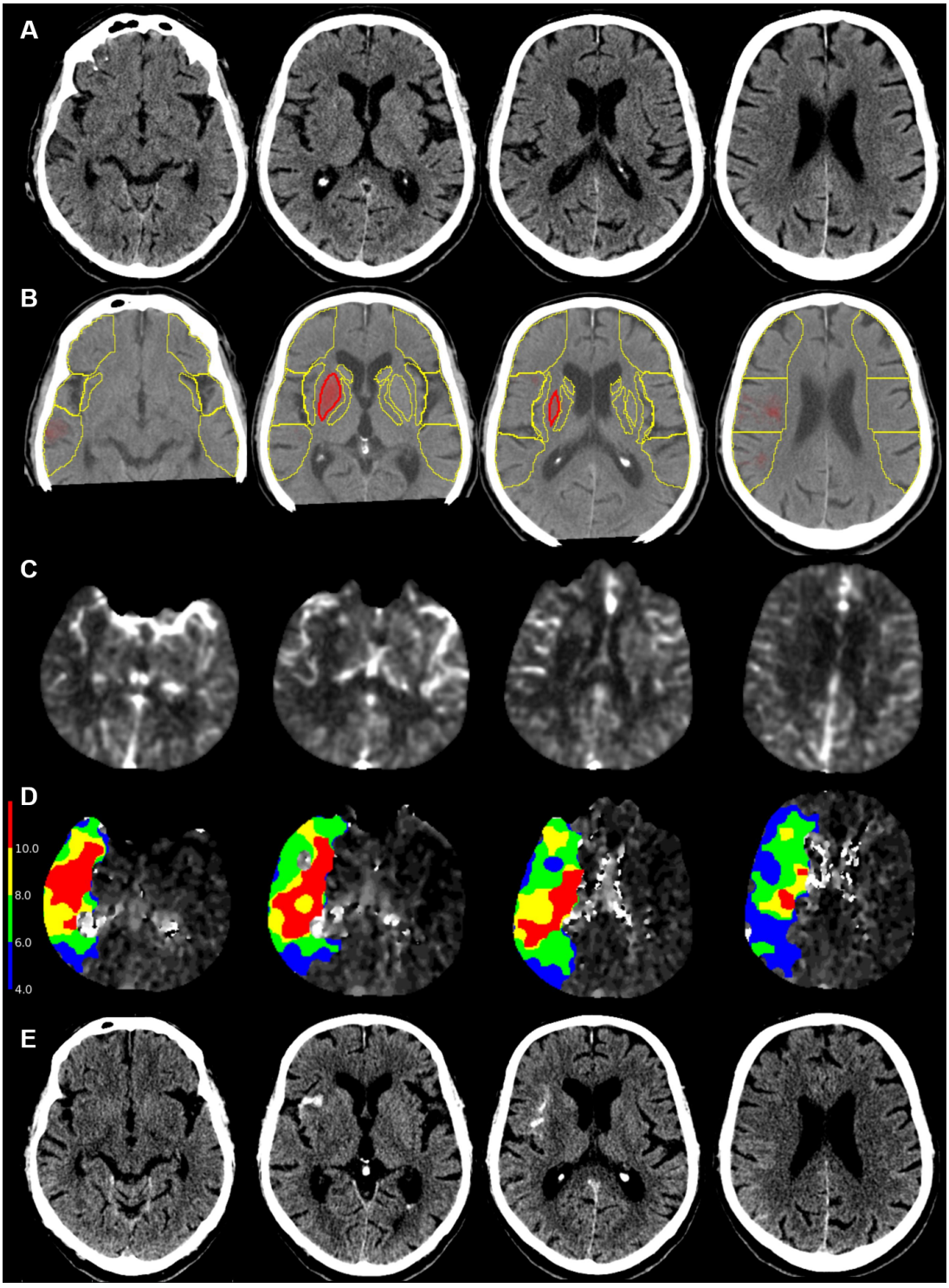
1.86 (median undercall was 0). The ASPECTS was rated as lower on baseline imaging in 15/81 cases for e-ASPECTS, 11/81 for expert consensus, 6/81 for CBF<30, and in 15/81 cases for Tmax>10s.

Sensitivity analysis

Clinical and imaging baseline characteristics for patients with determined successful recanalization were not significantly different in comparison to the subgroup of patients with non-determined recanalization (**Table 2)**. The results of the subgroup analysis in patients with successful reperfusion/recanalization are graphically demonstrated in **Figure 6** (**Table 3**). Accuracy of baseline ASPECTS and follow-up ASPECTS was 0.79 for e-ASPECTS, 0.81 for expert consensus, 0.83 for CBF<30% and 0.82 for Tmax>10s. Sensitivity and specificity were 0.51 and 0.90 for e-ASPECTS; 0.53 and 0.92 for expert consensus; 0.55 and 0.94 for CBF<30%; 0.66 and 0.89 for Tmax>10s, respectively. PPV and NPV were 0.67 and 0.82 for e-ASPECTS; 0.73 and 0.83 for expert consensus; 0.77 and 0.84 for CBF<30%; 0.7 and 0.87 for Tmax>10s, respectively.

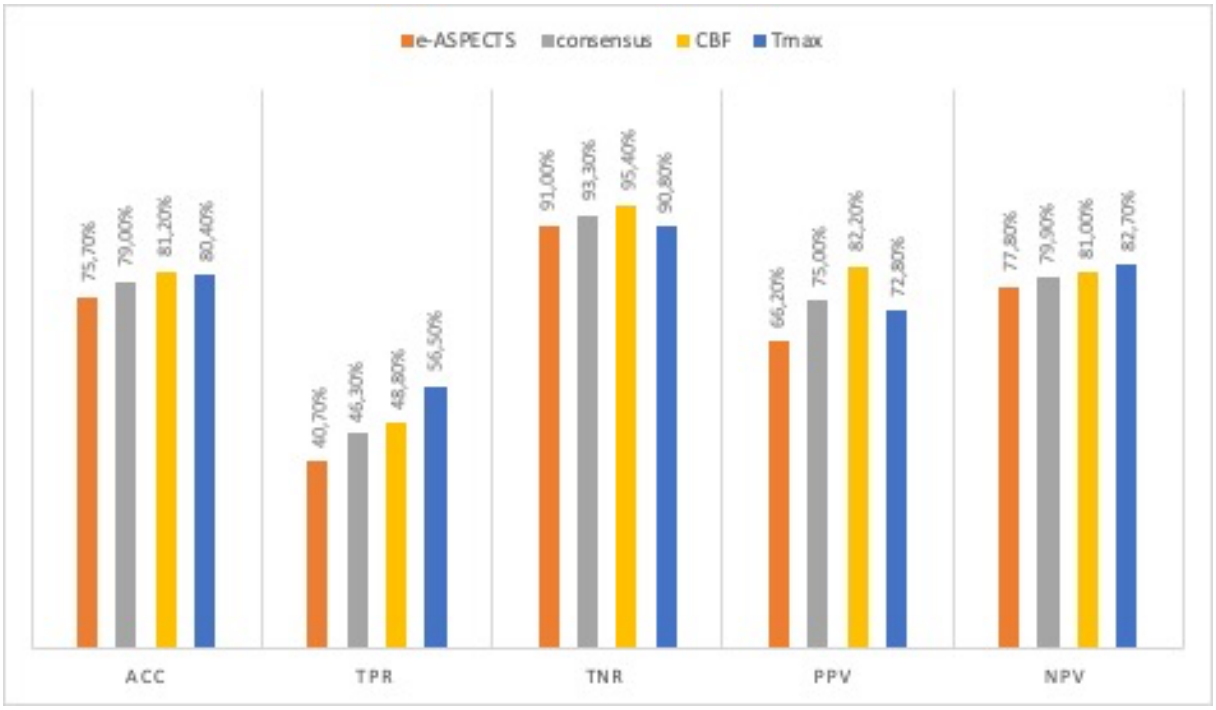
Bland-Altman plots for the subgroup analysis comparing differences in scores of baseline ASPECTS and follow-up ASPECTS are demonstrated in **Figure 7**. The mean difference between e-ASPECTS and follow-up was -0.70 ± 2.48 (median undercall of ASPECTS was -1), expert consensus and follow-up -0.79 ± 2.33 (median undercall was 0), CBF<30% and follow-up -0.82 ± 1.77 (median undercall was -1), and Tmax>10s and follow-up -0.21 ± 1.74 (median undercall was 0). The ASPECTS was lower on baseline imaging in 7/33 cases for e-ASPECTS, 6/33 for expert consensus, 5/33 for CBF<30% , and in 9/33 cases for Tmax>10s. There was no significant difference between residuals of the follow-up ASPECTS and each baseline ASPECTS for the two subgroups (determined recanalization versus non-determined recanalization group), the median undercall of baseline ASPECT scores was -1 point in comparison to the follow-up ASPECTS for the baseline methods in the subgroup with non-determined recanalization and for CBF<30% and e-ASPECTS in the subgroup with determined recanalization. There was a trend observed for Tmax>10s that show a higher precision in the subgroup with determined successful recanalization with the median undercall of 0 points. (**Table 4**). Results from generalized mixed model are illustrated in **Figure 8**.

Figure 3: Comparison of CT imaging modalities and evaluation of early ischemic changes



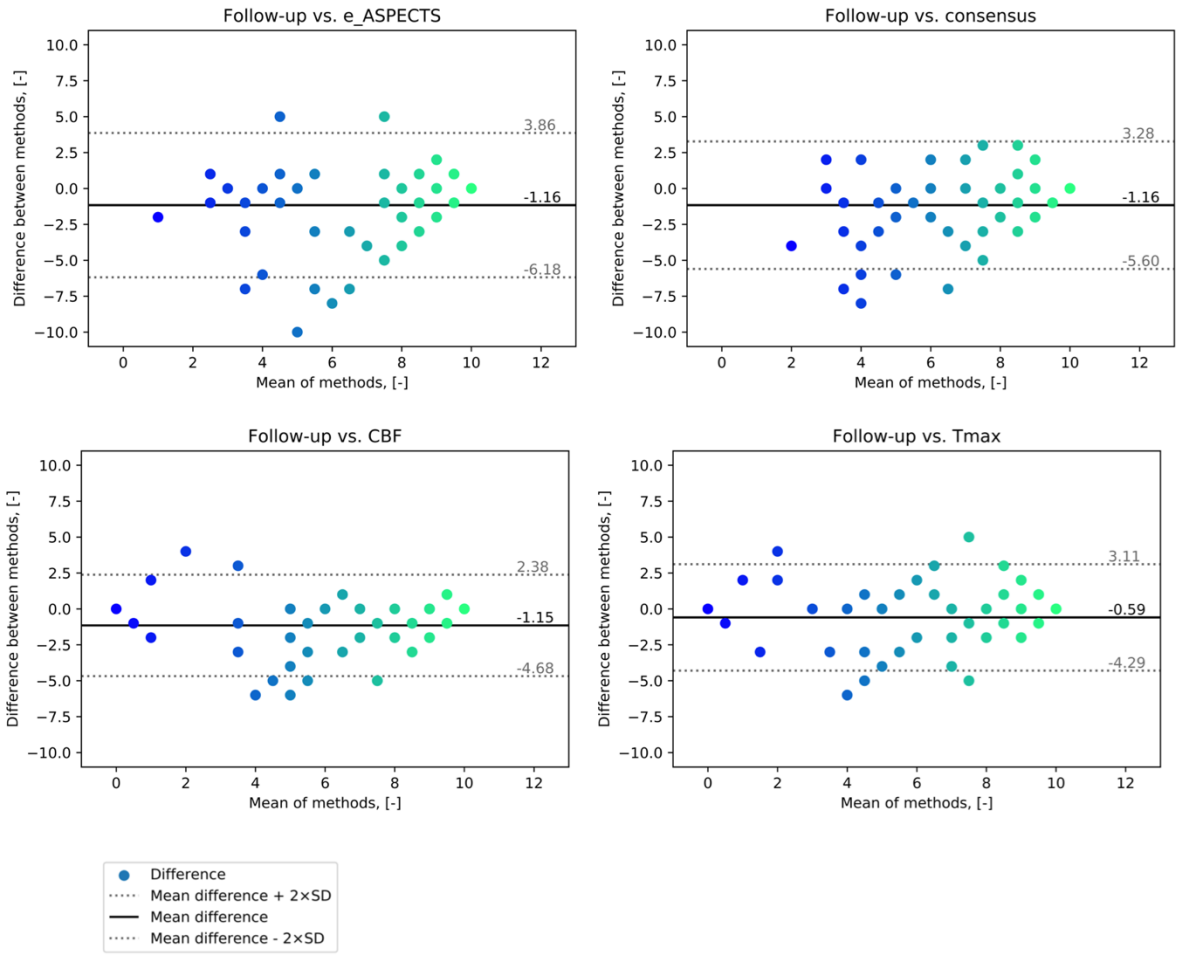
Legend: Baseline ASPECTS was assessed as follows: 10 points on NCCT by expert reading (A), 9 (lentiform) by automatic e-ASPECTS (B) and 6 (M2, M3, insula, lentiform) on Tmax>10s CTP maps (C). Follow-up CT (D) shows the ischemic changes within insula, lentiform and M5 (ASPECTS 7); and hemorrhagic transformation within the right insula.

Figure 4: Accuracy, sensitivity, specificity, positive predictive value, negative predictive value of baseline ASPECTSs evaluated by e-ASPECTS, consensus (expert reading), CBF<30% and Tmax>10s)



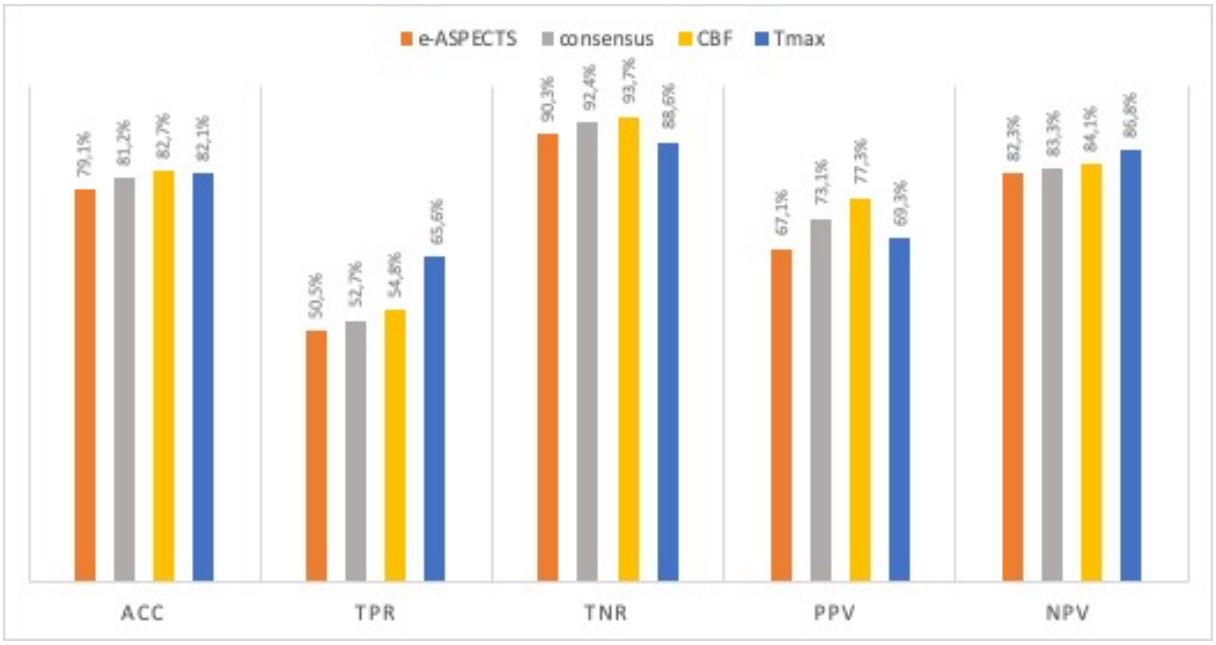
Legend: ACC – accuracy; TPR – true positive value/sensitivity, TNR – true negative value/specificity, PPV – positive predictive value, NPV – negative predictive value

Figure 5: Bland-Altman plots



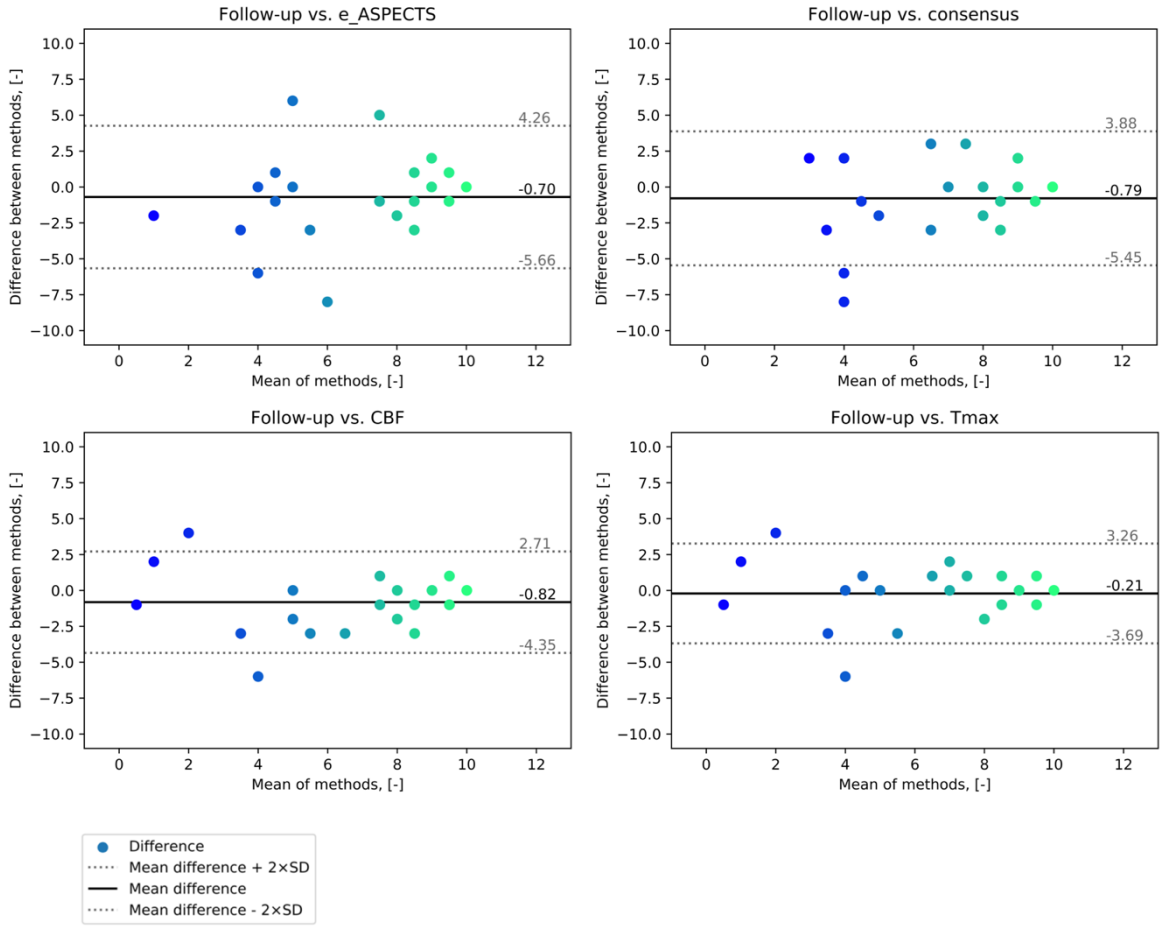
Legend: Bland-Altman plots illustrating the level of agreement between the baseline and follow-up ASPECTS for different baseline CT modalities and means of evaluation (software vs. expert reading). Solid line indicates the mean difference between the baseline and follow-up, dashed lines indicate the limits of the agreement.

Figure 6: Subgroup analysis of patients with successful reperfusion – accuracy, sensitivity, specificity, positive predictive value and negative predictive value for baseline assessment (e-ASPECTS, consensus, CBF<30% and Tmax>10s) and final ischemic changes on follow-up NCCT



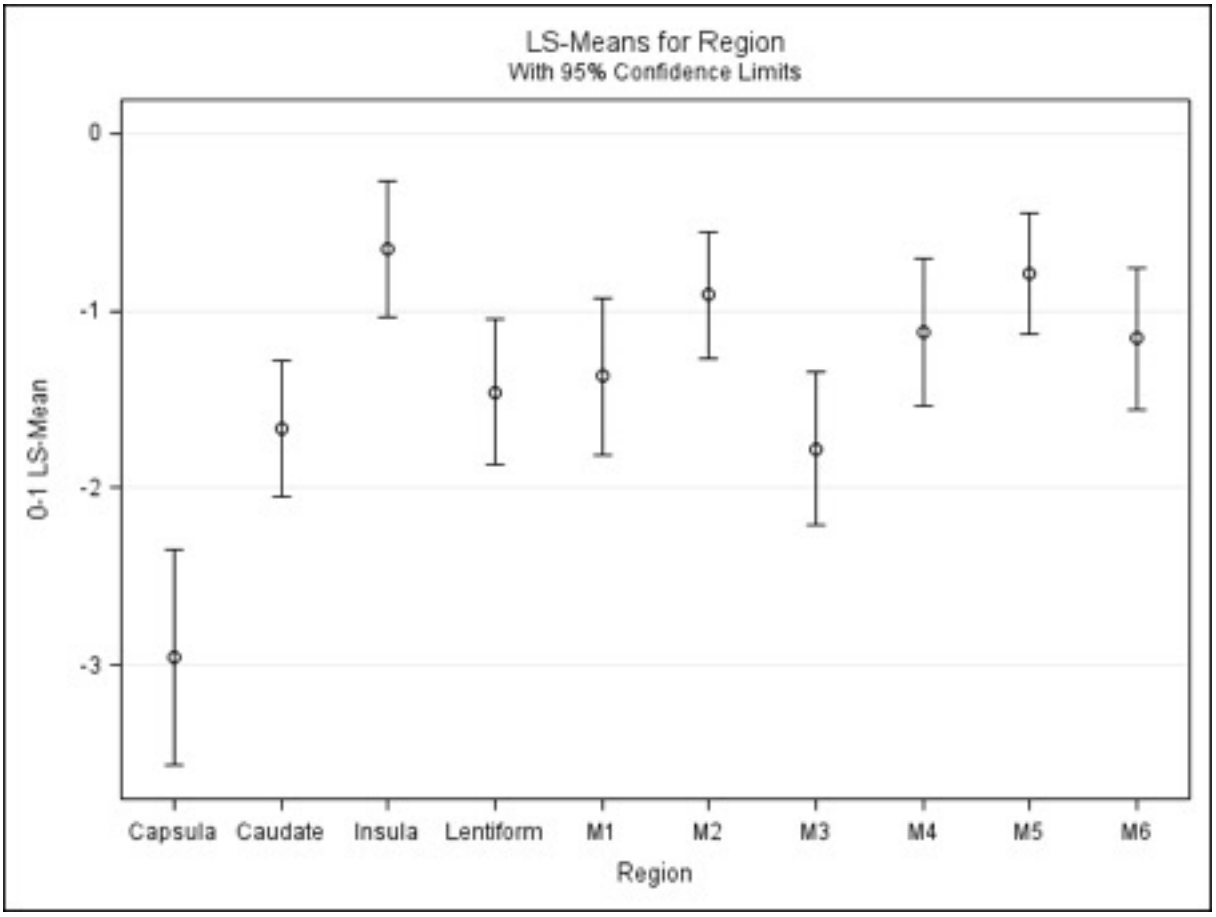
Legend: ACC – accuracy; TPR – true positive value/sensitivity, TNR – true negative value/specificity, PPV – positive predictive value, NPV – negative predictive value

Figure 7: Bland-Altman plots for the subgroup analysis of patients with successful recanalization/reperfusion (MT and IVT group pooled data)



Legend: Bland-Altman plots compare the baseline ASPECTS and follow-up ASPECTS for baseline CT modalities and different means of assessment. Solid line indicates the mean difference between baseline and follow-up, dashed lines indicate the limits of the agreement.

Figure 8: Least square means estimates of fixed effect "region" computed from generalized mixed model



Legend: The least square means (Ls-means) estimates were computed from a generalized mixed model (fixed effect was ASPECTS region). Follow-up NCCT was used as a reference grid. Results expressed on a logit scale demonstrate the highest agreement for final ischemia in insula and M5 region regardless the used CT modality and scoring approach. The lowest odds were demonstrated for internal capsule, which also showed the highest variability in scoring.

Table 1: Accuracy, sensitivity, specificity, PPV and NPV of baseline ASPECTS (e-ASPECTS, consensus, CBF<30% and Tmax>10s) vs. follow-up imaging

	Accuracy	Sensitivity	Specificity	PPV	NPV
e-ASPECTS vs. follow-up	0.76	0.41	0.91	0.66	0.78
Consensus vs. follow-up	0.79	0.46	0.93	0.75	0.8
CBF<*30%* vs. follow-up	0.81	0.49	0.95	0.82	0.81
Tmax>10 s vs. follow-up	0.80	0.57	0.91	0.73	0.83

Legend: ASPECTS = Alberta Stroke Program Early CT Score; CBF = cerebral blood flow; NPV = negative predictive value; PPV = positive predictive value; Tmax = time to maximum.

Table 2: Comparison of patient baseline characteristics for the whole dataset (n=81) and a subgroup of patients with determined successful recanalization (n=33)

	Dataset N= 81	Recanalization subgroup N=33	P-value*
Female sex – n (%)	38 (46.9)	13 (39.4)	0.26
Age – median (IQR)	71 (62 – 81)	69 (62 – 80)	0.54
Affected left side – n (%)	44 (54.3)	18 (54.55)	0.97
Baseline NIHSS – median (IQR)	9 (4 – 17)[1]	14 (7 – 17.5)[1]	0.002
Baseline ASPECTS – median (IQR)	9 (7 – 10)	9 (6.5 – 10)	0.41
Onset to baseline CT in min – median (IQR)	156 (71-220)[2]	110 (67-216)[2]	0.41

Legend: IQR = interquartile range, NIHSS = National Institutes of Health Stroke Scale, ASPECTS = Alberta Stroke Program Early CT Score, EVT = endovascular treatment

*Derived from Wilcoxon rank sum test for two subgroups – determined successful recanalization versus non-determined recanalization

[1] computed for n=79 and subgroup n=32

[2] computed for n=69 and subgroup n=31

Table 3: Subgroup analysis of patients with successful reperfusion/recanalization – accuracy, sensitivity, specificity, PPV and NPV of baseline ASPECTSs (e-ASPECTS, consensus, CBF<30% and Tmax>10s) vs. follow-up imaging

	Accuracy	Sensitivity	Specificity	PPV	NPV
e-ASPECTS vs. follow-up	0.79	0.51	0.93	0.67	0.82
Consensus vs. follow-up	0.81	0.53	0.92	0.73	0.83
CBF<*30%* vs. follow-up	0.83	0.55	0.94	0.77	0.84
Tmax>10 s vs. follow-up	0.82	0.66	0.89	0.69	0.87

Legend: ASPECTS = Alberta Stroke Program Early CT Score; CBF = cerebral blood flow; NPV = negative predictive value; PPV = positive predictive value; Tmax = time to maximum.

Table 4: Comparison of residuals for the follow-up ASPECTS and the baseline ASPECTS for the subgroups of patients with determined successful recanalization versus non-determined recanalization

	Determined recanalization n=33	Non-determined recanalization n=48	p-value*
e-ASPECTS – median (IQR)	-1 (-3 – 0)	-1 (-1 – 0)	0.54
Consensus – median (IQR)	-1 (-2.5 – 0)	0 (-2 – 0)	0.15
CBF <30% – median (IQR)	-1 (-2 – 0)	-1 (-2 – 0)	0.26
Tmax >10s – median (IQR)	-1 (-2 – 0)	0 (-1 – 1)	0.03

Legend: ASPECTS = Alberta Stroke Program Early CT Score; CBF = cerebral blood flow; Tmax = time to maximum.

*Derived from Wilcoxon rank sum test

Discussion

In this study we demonstrated high sensitivity and specificity for detection of acute ischemic changes for CT imaging modalities including assessment of acute ischemic changes by experienced readers and clinically available software. Unlike in previous studies, we have focused on CTP parameters representing either ischemic core (CBF<30%) or severely hypoperfused tissue (Tmax>10s), parameters that were not analyzed previously in the perspective of ASPECT scoring. CBF <30% is nowadays widely accepted to represent the ischemic core with the high sensitivity and specificity and with low overestimation of the core, that could result in unwarranted exclusion of patients who could benefit from reperfusion. (29) In contrast to Tmax>6s, which is used to define penumbra, we evaluated a more severe delay, Tmax>10s, representing the critically hypoperfused tissue, which is associated with irreversible necrosis of the ischemic lesion even after reperfusion. (33)

The highest specificity was observed for CTP parameter, rCBF<30%, assessed visually on CTP maps processed by RAPID software. This CTP parameter also showed the highest positive predictive value for final ischemic changes. Moreover, the CTP parameter of Tmax delay >10s, representing a severe hypoperfusion, showed the highest sensitivity and high accuracy for prediction of final ischemic lesion (within the whole dataset as well as in the subgroup analysis of successful reperfusion/recanalization). Tmax delay >10s was studied previously – the association of large Tmax>10s lesion and malignant MCA profile was showed in previous studies. (30) (36) Tmax volumes at a delay of >8s and >10s were strongly correlated with clinical outcome. (37) Our findings support the importance of this parameter in the detection of irreversible ischemic changes on baseline neuroimaging. We demonstrated that both CBF <30% and Tmax>10s have high accuracy in detection of early ischemic changes as shown previously for CBV and these changes could be easily assessed on the derived perfusion maps from RAPID analysis. (25) (26) (27) (28)

The Blant-Altman plots showed the lowest difference in baseline ASPECTS and follow-up ASPECTS for Tmax>10s. The other baseline methods showed similar differences in baseline and follow-up ASPECTS with the median undercall of the baseline score of 1 point (these findings did not differ when we analyzed the residuals between follow-up ASPECTS and baseline

ASPECTS for the subgroups with determined/non-determined recanalization). The CBF <30% and Tmax>10s also demonstrated the lowest data dispersion for baseline and follow-up ASPECTS. This indicates that these perfusion parameters may represent irreversibly affected tissue with higher accuracy in comparison to detectable changes on baseline NCCT. Nevertheless, the semi-automated analysis showed similar results with expert reading. This finding suggests a comparable diagnostic value of the software evaluation and expert reading in the acute stroke management. Although e-ASPECTS showed the lowest accuracy and sensitivity among the tested baseline methods, the accuracy of 0.76 could still be considered as good, the sensitivity analysis also did not show any significant difference between baseline methods for the tested subgroups. The comparable findings for e-ASPECTS and other studied imaging methods implicates the benefit of software evaluation for less experienced readers.

We observed a certain level of variability in assessment of particular ASPECTS regions. The highest odds for agreement in evaluation of baseline ischemic changes and final ischemia was demonstrated for insula regardless the baseline imaging modality and the way of ASPECT scoring. It was demonstrated previously that the insular ribbon sign represented a very early ischemic change in the middle cerebral artery strokes. (38) Contrarily, the lowest odds for agreement between multimodal baseline and follow-up imaging was observed in the internal capsule. That might be explained by difficulties in the visual assessment of hypoattenuation within this region as the internal capsule is naturally less hypodense on NCCT. (39) This small subcortical region might also be challenging to be distinguished on the CTP maps as hypoperfused. Additionally, there was low variability demonstrated for all cortical ASPECTS regions, caudate and lentiform. It may reflect that early ischemic changes of the insula are easy to detect even with the low experience, but assessment of early ischemic changes within the internal capsule might be problematic also for experienced readers.

We are aware of some limitations of this study. First of all, this was a single center observational study. The patients were not selected according to the recanalization rate. Information about the recanalization status was available only in patients indicated to mechanical thrombectomy. Nevertheless, due to a limited (6-months) period when the e-ASPECTS software was available at our institution, we decided to include all patients meeting our inclusion criteria

regardless of the treatment or recanalization status. We also did not focus on the correlation of ASPECTS and final clinical outcome, as this relationship has been studied in other work.(40) The main purpose of this work was to evaluate the accuracy of ASPECTS assessment on baseline multimodal imaging. We are also aware of a possible misinterpretation of particular regions caused by visual application of ASPECTS regions into the CTP maps processed by RAPID software. At the time of the patient recruitment, the RAPID CTP software presented only the volumes of impaired tissue perfusion (not co-registered within the ASPECTS regions). The automatic segmentation of ASPECTS regions on e-ASPECTS scans also has its limitations and beside the visual control to avoid any severe inaccuracy we did not tend to correct the automatic segmentation and given ASPECTS scoring as we aimed to test the accuracy of commercially available version of the software.

There are a few potential pitfalls in regard of the detection of acute ischemic changes with automatic analysis. There might be a false positive finding on CTP maps in patients with a subacute or chronic infarction. The RAPID software automatically segments and removes areas with very low CBF, such as CSF spaces and other extra-parenchymal tissue, so in most cases subacute/chronic infarction is also excluded. Another known pitfall is that CTP maps do not display an infarcted area if the reperfusion was achieved ahead of the imaging, even though there is evidence of the infarction on NCCT. These potential pitfalls highlight the necessity of a visual control of CTP derived maps with NCCT or other available imaging as well as a control of the correct placement of arterial input function and venous output function.

Section 2.2 – Utility of Time-Variant Multiphase CTA Color Maps in Outcome Prediction for Acute Ischemic Stroke Due To Anterior Circulation LVO

Based upon: OSPEL, Johanna M., Petra CIMFLOVA, **Ondrej VOLNY**, Wu QIU, Moiz HAFEEZ, Arnuv MAYANK, Mohamed NAJM, Kevin CHUNG, Nima KASHANI, Mohammed A. ALMEKHLAFI, Bijoy K. MENON a Mayank GOYAL. Utility of Time-Variant Multiphase CTA Color Maps in Outcome Prediction for Acute Ischemic Stroke Due to Anterior Circulation Large Vessel Occlusion. *Clinical Neuroradiology* [online]. 2020. ISSN 1869-1439.

Abstract

Background – mCTA is an established tool for EVT decision-making and outcome prediction in acute ischemic stroke. We aimed to determine whether mCTA-based prediction of clinical outcome and final infarct volume can be improved by assessing collateral status on time-variant mCTA color maps rather than using a conventional mCTA display format.

Methods – Patients from the PRove-IT cohort study with anterior circulation LVO were included in this study. Collateral status was assessed with a three-point scale using the conventional display format. Collateral extent and filling dynamics were then graded on a three-point scale using time-variant mCTA color-maps. Multivariable logistic regression was performed to determine the association of conventional collateral score, color-coded collateral extent and color-coded collateral filling dynamics with good clinical outcome and final infarct volume.

Results – A total of 285 patients were included in the analysis and 53% (152/285) of the patients achieved a good outcome. Median infarct volume on follow-up was 12.6 ml. Color-coded collateral extent was significantly associated with good outcome (adjusted odds ratio [adjOR] 0.53, 95% confidence interval [CI]:0.36–0.77) while color-coded collateral filling dynamics (adjOR 1.30 [95% CI:0.88–1.95]) and conventional collateral scoring (adjOR 0.72 [95%CI:0.48–1.08]) were not. Both color-coded collateral extent (adjOR 2.67 [95%CI:1.80–4.00]) and conventional collateral scoring (adjOR 1.84 [95%CI:1.21–2.79]) were significantly associated with follow-up infarct volume, while color-coded collateral filling dynamics were not (adjOR 1.21 [95%CI:0.83–1.78]).

Conclusion – Collateral extent assessment on time-variant mCTA maps improved prediction of good outcome and has similar value in predicting follow-up infarct volume compared to conventional mCTA collateral grading.

Introduction

Acute ischemic stroke due to LVO is a highly time-critical disease. In 2015, EVT became the standard of care for LVO strokes presenting within 6 hours from symptom onset. There are many ways of identifying irreversibly damaged tissue; the most commonly used imaging techniques are CT perfusion and mCTA. Both techniques have been successfully used for EVT patient selection in randomized controlled trials. (14) (15) (2) (16) We have recently described a new color-coded mCTA display format, in which all 3 mCTA series are consolidated in a single color-coded map, thereby potentially facilitating and improving mCTA interpretation. (41) The purpose of this study was to compare prediction of clinical outcome and final infarct volume in acute ischemic stroke due to LVO using a conventional mCTA display format vs. time-variant color maps.

Methods

Patient Population

The Precise and Rapid Assessment of Collaterals Multiphase CTA in the Triage of Patients with Acute Ischemic Stroke for IA Therapy (Prove-IT) study was a prospective multicenter cohort study that enrolled 464 patients who presented with symptoms consistent with AIS (NCT02184936). Patients were eligible for the study if they presented to the emergency department with symptoms consistent with AIS, were older than 18 years, and mCTA and CTP were performed within 12 hours of symptom onset and before recanalization therapy. We included patients with anterior circulation LVO (internal carotid artery, M1 or proximal M2 MCA occlusions). Enrolled patients in who baseline NCCT and mCTA images were incomplete or not interpretable were excluded from this analysis.

Image Acquisition

NCCT and mCTA: NCCT was acquired with 5 mm slice thickness. The mCTA scans consisted of three phases, with arch to vertex coverage in the first (arterial) and skull base to vertex coverage the second (peak venous) and third (late venous) phases. Detailed mCTA acquisition parameters have been published previously.(17) Axial images with 1 mm overlap and multiplanar axial, coronal and sagittal reconstructions with 3 mm thickness, 1 mm intervals and 1 mm overlap for the first phase were then generated as well as axial maximum intensity projections (MIPs)

for all three phases. Time variant mCTA color maps were generated with the FastStroke research prototype (GE Healthcare, Milwaukee, WI, USA) and displayed as axial, coronal, sagittal, and oblique MIP reformations. Color-coding of the collaterals is hereby based on a per-patient adaptive threshold technique; vessels with maximum enhancement in the pre-venous phase are displayed in red, those with maximum enhancement in the peak venous phase and late venous phase are displayed in green and blue, respectively (**Figure 2**). (41)

Image Interpretation

All images were assessed in a consensus reading (by a neurologist OV and neuroradiologist JO). ASPECTS was scored on 5 mm reconstructed axial unenhanced NCCT images. Occlusion site was determined on axial mCTA MIP images and was reported as either terminal internal carotid artery, M1 segment or proximal M2 segment. We decided to include the proximal M2 segment in our analysis, since most physicians consider proximal M2 occlusions as LVO and as appropriate target lesions for EVT. (42) Proximal M2 occlusions were hereby defined as Sylvian segment M2 occlusions located within 1 cm from the MCA bifurcation.

Conventional mCTA Collateral Grading: The delay and extent of collateral filling was graded on axial MIPs of the three mCTA phases. A trichotomized collateral scale as used in the ESCAPE (2) and ESCAPE NA1 (43) trials was applied:

Poor collaterals: no or only few vessels visible in any phase within the occluded vascular territory compared to the asymptomatic contralateral hemisphere.

Intermediate collaterals: delay of two phases in filling in of peripheral vessels or a one-phase delay and some ischemic regions with only few or no vessels compared to the asymptomatic contralateral hemisphere.

Good collaterals: no delay or 1 phase delay in filling of peripheral vessels with identical or increased prominence of vessels compared to the asymptomatic contralateral hemisphere.

Collateral Grading on Time-variant Color Maps: Both delay and extent of collateral filling were graded on a trichotomized scale on axial color-coded MIPs. In other words, in the color-map based assessment, two separate scores were applied for collateral filling dynamics and collateral extent,

as opposed to conventional mCTA scoring, in which both of these factors were graded in a single score.

Collateral extent was graded as follows:

Normal or almost normal extent (>90%) of visible vessels within the occluded vascular territory compared to the contralateral hemisphere.

Vessel extent 50–90% within the occluded vascular territory compared to the contralateral hemisphere.

Vessel extent <50% within the occluded vascular territory compared to the contralateral hemisphere.

Collateral delay was graded as follows:

Predominantly no delay (most vessels are displayed in red) within the occluded vascular territory.

Predominantly 1 phase delay (most vessels are displayed in green) within the occluded vascular territory.

Predominantly 2 phase delay or no collaterals (most vessels are displayed in blue/no vessels visible at all) within the occluded vascular territory.

Follow-up infarct volumes were measured by summation of manual planimetric demarcation of infarct on axial NCCT or diffusion-weighted imaging magnetic resonance imaging (DWI-MRI) follow-up imaging at 24-32 h.

Interrater Agreement

To determine interrater agreement for scoring of collateral extent and filling dynamics on time-variant mCTA color maps, a neuroradiologist and a medical student independently reviewed 30 cases in 2 separate reading sessions with a 1-week break between the sessions (session 1: conventional collateral scoring, session 2: assessment of collateral extent and filling dynamics on time-variant color maps). The readers had access to the site of occlusion, age and baseline National Institutes of Health Stroke Scale (NIHSS), but they were blinded to all other baseline information and patient outcomes.

Statistical Analysis

Patient baseline characteristics were described using descriptive statistics. Univariable and multivariable logistic regression was used to determine the association of conventional and color-coded collateral scores and a) good outcome, defined as mRS 0–2 at 90 days (primary outcome), and b) follow-up infarct volume (secondary outcome). Follow-up infarct volume was hereby included in the models as binary variable (infarct volume below or equal to vs. above the median infarct volume in the study sample). Information loss across models was compared using the Akaike and Bayesian information criteria (AIC, BIC) and the area under the curve (AUC). Adjustment was performed for patient age, sex and baseline NIHSS. Since the follow-up imaging modality could influence follow-up infarct volume measurements; sensitivity analysis was performed for follow-up infarct volume as dependent variable for patients with NCCT vs. DWI-MRI follow-up imaging. Interrater agreement was assessed using the Kappa statistics. All statistical tests were two-sided and conventional levels of significance (alpha=0.05) were used for interpretation. All analysis was performed using Stata 15.1 (Stata Corp LLC, College Station, TX, USA).

Results

Out of 464 patients 285 were included in the analysis. When using the trichotomized grading system on conventional display format, 60.7% (173/285) patients had good collaterals, 30.2% (86/285) had intermediate and 9.1% (26/285) poor collaterals. Collateral extent on time-variant color maps was normal or almost normal in 50.9% (145/285) patients, a collateral extent of 50–90% compared to the contralateral hemisphere was seen in 34.0% (97/285), and a collateral extent of less than 50% compared to the contralateral hemisphere in 15.1% (43/285). When using time-variant color maps, there was mostly no delay in 14.4% (41/285), mostly a one-phase delay in 56.5% (161/285) and mostly a two-phase delay in 29.1% (83/285).

Collateral Grading and Clinical Outcome

Overall, 53.3% of patients (152/285) achieved a good outcome at 90 days. **Table 5** shows unadjusted and adjusted measures of effect size for the association of conventional collateral grade, color-coded collateral extent, color-coded collateral filling dynamics and good clinical outcome, as well as the respective AIC, BIC, and AUC values for the multivariable models.

Collateral Grading and Follow-up Infarct Volume

Infarct volume was available for 93.0% (265/285) patients. Median final infarct volume was 12.6 ml (IQR 1.7–49.2). **Table 6** shows unadjusted and adjusted measures of effect size for the association of conventional collateral score, color-coded collateral filling dynamics, color-coded collateral extent and follow-up infarct volume (infarct volume equal to or below vs. above the median infarct volume), as well as the respective AIC, BIC, and AUC values for the multivariable models. Interrater agreement for color-coded grading of collateral filling dynamics and collateral extent was substantial (Kappa=0.69 and 0.74, respectively).

Table 5: Association of conventional and color-map based collateral grade and good clinical outcome (*N* = 285)

Collateral score	Unadjusted OR (95% CI)	Adjusted OR [a] (95% CI)	AIC [b]	BIC [b]	AUC [b] (95% CI)
Conventional score	0.62 (0.43–0.89)	0.72 (0.48–1.08)	350.0	368.2	0.74 (0.69–0.80)
Color-map based collateral extent	0.54 (0.39–0.75)	0.53 (0.36–0.77)	340.9	359.2	0.76 (0.70–0.81)
Color-map based filling delay	1.21 (0.84–1.74)	1.30 (0.88–1.95)	350.8	369.1	0.74 (0.68–0.80)

Legend: *OR* odds ratio, *95% CI* 95% confidence interval, *AIC* Akaike information criterion, *BIC* Bayesian information criterion, *AUC* area under the curve

[a]Adjusted for patient age, sex and baseline National Institutes of Health Stroke Scale

[b]Derived from adjusted models

Table 6: Association of conventional and color-map based collateral grade and final infarct volume (*N* = 265)

Collateral score	Unadjusted OR (95% CI)	Adjusted OR [a] (95% CI)	AIC [b]	BIC [b]	AUC [b] (95% CI)
Conventional score	2.05 (1.37–3.07)	1.84 (1.21–2.79)	354.2	372.1	0.67 (0.60–0.73)
Color-map based collateral extent	2.99 (2.04–4.40)	2.67 (1.80–4.00)	336.4	354.3	0.72 (0.66–0.78)
Color-map based filling delay	1.29 (0.89–1.87)	1.21 (0.83–1.78)	361.7	379.6	0.63 (0.57–0.70)

Legend: Final infarct volume was coded as a binary variable in this analysis (volume below vs. above the median infarct volume)

OR odds ratio, *95% CI* 95% confidence interval, *AIC* Akaike information criterion, *BIC* Bayesian information criterion, *AUC* area under the curve

[a]Adjusted for patient age, sex and baseline National Institutes of Health Stroke Scale.

[b]Derived from adjusted models

Discussion

Our study has the following main findings: 1) color-coded mCTA grading of collateral extent improves prediction of good outcome at 90 days, and its performance in predicting follow-up infarct volume is similar compared to conventional collateral grading, 2) color-coded mCTA grading of collateral filling dynamics performs worse than conventional collateral grading and 3) interrater agreement for color-coded mCTA grading of collateral extent and filling dynamics is substantial.

Assessing collateral status on mCTA using a conventional display format, i.e. three separate series that are usually linked by the reader and then assessed in conjunction, takes both collateral filling dynamics and extent into account. (44) When using time-variant mCTA color maps, collateral extent and filling dynamics are graded separately. When color-coded collateral extent was used to predict good outcome and follow-up infarct volume in our study, information loss was lower and discrimination better compared to conventional mCTA collateral scoring and color-coded scoring of filling dynamics. These results potentially indicate that collateral extent reflects tissue viability more accurately compared to collateral filling dynamics. In a previous study, d'Esterre et al. assessed collateral extent and filling dynamics on conventional mCTA images and found that the former was not independently associated with follow-up infarction, while washout, a parameter that partly reflects filling dynamics, was associated with follow-up infarction. (45) The apparently contradictory findings between their study and our study could be explained by the fact that in the current study, the entire hemisphere was assessed, while d'Esterre et al. evaluated brain tissue per ASPECTS region. Both the current study and the study by d'Esterre et al. relied on visual assessment of collaterals, which will always be subject to some degree of interrater variability. This variability could also explain the different results. Automation of collateral scoring could mitigate this problem, but the automated assessment would have to be available instantaneously, and integration of the technology into routine clinical practice will take some time. (46) Software to generate time-variant mCTA maps on the other hand is already available, and the color-maps can be generated within a few seconds. mCTA color-maps therefore constitute a good alternative to facilitate interpretation of collateral status until fully automated collateral assessment becomes routinely available, particularly for less experienced readers. Indeed, when comparing a non-expert to an expert reader, interrater agreement for color-map based

collateral grading in our study was substantial. Agreement was higher for color-map based grading of collateral extent compared to filling dynamics. This suggests that the latter is more challenging, which could be the reason for the lacking association of collateral filling dynamics and clinical outcome/follow-up infarct volume. The predictive utility of conventional collateral assessment, while it was still good overall, was slightly lower when compared to color-map based grading of collateral extent. It is possible that complications that happened after treatment in the 3-month follow-up period have influenced the association with clinical outcomes, while the efficacy of treatment (either EVT or IVT) might have influenced the association of collateral grade and follow-up infarct volumes, although the latter two points would in theory affect both conventional and color-map based collateral grading. The exact reasons for the differences in predictive power remain therefore unknown at the time being.

Limitations

Our study has several limitations: First, assessing infarct volumes on NCCT can be challenging, since the infarct is often not clearly demarcated. Second, we restricted our analysis to patients with LVO (including proximal M2 occlusions); our findings can thus not be generalized to more distal occlusion sites. Third, reperfusion status is an important predictor of infarct volume and outcome, but since vascular imaging was not available in all patients, we could not stratify our analysis by reperfusion status. Fourth, recanalization data were missing in a relatively large number of patients, partly because it was impractical to obtain follow-up vascular imaging in many local institutional settings, and partly because it does not have a therapeutic consequence in the vast majority of cases. Fifth, we showed that color-map based assessment of collateral extent is significantly associated with good outcome and infarct volume in LVO patients, but we could not assess in our study whether and how this alters clinical decision-making. Doing so would warrant a diagnostic randomized controlled trial. Such trials generally require very large sample sizes and are difficult to conduct for various reasons. (47)

Section 3 – Endovascular Treatment of Acute Ischemic Stroke

The treatment of AIS has undergone very dramatic changes in last decade. Randomized trials demonstrated that EVT represents a highly effective and safe treatment. In order to confirm the broad applicability of EVT in the anterior circulation LVO strokes and to establish the treatment effect at a national level, we compared the Czech EVT data with the patient-level HERMES meta-analysis pooling data from the five randomized controlled trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA). Section 3.1 is devoted to this topic in detail.

EVT represents a standard of care for AIS due to LVO, but level 1A guideline recommendations for EVT are currently restricted to LVO patients with NIHSS $\geq$ 6. AIS with NIHSS $\leq$ 6 is routinely considered as "mild" and/or "non-disabling". However, one in four patients with low baseline NIHSS suffer early neurologic deterioration. The aim of our observational multicenter study was to assess the effectiveness and safety of EVT versus best medical management in patients with CTA detected LVO in the anterior circulation and NIHSS $\leq$ 6 using recent data from comprehensive datasets and propensity score matching. Section 3.2 is devoted to this topic in detail.

Additionally, the **ANNEX 3** is dedicated to our single-centre experience with patients' selection for EVT based on automated CTP analysis and it also compares our results with CTP-based randomized controlled trials. The **ANNEX 4** represents the first comprehensive nationwide questionnaire-based evaluation of all stroke centres in the Czech Republic performing EVT in 2016. The **ANNEX 5** summarizes the technical EVT results from the year of 2016.

Section 3.1 – Mechanical Thrombectomy Performs Similarly in Real-World Practice: A 2016 Nationwide Study from the Czech Republic

Based upon: VOLNY, Ondrej, Antonin KRAJINA, Silvie BELASKOVA, Michal BAR, Petra CIMFLOVA, Roman HERZIG, Daniel SANAK, Ales TOMEK, Martin KOCHER, Miloslav ROCEK, Radek PADR, Filip CIHLAR, Miroslava NEVSIMALOVA, Lubomir JURAK, Roman HAVLICEK, Martin KOVAR, Petr SEVCIK, Vladimir ROHAN, Jan FIKSA, Bijoy K. MENON a Robert MIKULIK. Mechanical thrombectomy performs similarly in real world practice: a 2016 nationwide study from the Czech Republic. *Journal of Neurointerventional Surgery* [online]. 2018, **10**(8), 741–745. ISSN 1759-8478.

Abstract

Background – Randomized clinical trials have proven EVT to be a highly effective and safe treatment in acute stroke. The purpose of this study was to compare EVT data from the Czech Republic (CR) with data from the HERMES meta-analysis.

Methods – Available nationwide data for the CR from the year 2016 from the SITS-TBY registry on patients with terminal internal carotid artery (ICA) and/or MCA occlusions were compared with data from the HERMES pooled dataset. CR and HERMES patients were comparable in age, sex and baseline NIHSS scores.

Results – From a total of 1,053 EVTs performed in the CR, 845 (80%) were reported in the SITS-TBY. From these, 604 (72%) were included in this study. Occlusion locations were as follows (CR vs. HERMES): ICA 22% vs. 21% (p=0.16), M1 MCA 62% vs. 69% (p=0.004), M2 MCA 16% vs. 8% (p<0.0001). Intravenous thrombolysis was given in 76% vs. 83% patients (p=0.003). Median onset-to-reperfusion times were comparable: 232 vs. 285 min (p=0.66). A modified TICI score of 2b/3 was achieved in 74% (433/584) vs. 71% (390/549) of the patients (OR=1.17, 95%CI=0.90-1.5, p=0.24). There was no statistically significant difference in percentage of PH type 2 (OR=1.12, 95%CI=0.66-1.90, p=0.68). A modified Rankin scale score of 0-2 at 3 months was achieved in 48% (184/268) vs. 46% (291/633) of the patients (OR=0.92, 95% CI=0.71-1.18, p=0.48).

Conclusions – Data on efficacy, safety and logistics of EVT from the CR is similar to data from the HERMES collaboration.

Introduction

Recent randomized trials have demonstrated that EVT with second-generation neurothrombectomy devices represents a highly effective and safe treatment for patients with AIS due to occlusion/s in the anterior cerebral circulation. (48) (2) (31) (49) (15) Data from the HERMES meta-analysis have proven the degree of benefit of this procedure to be substantial; for every 100 patients treated, 38 will have a less disabled outcome than those who receive the best possible medical treatment, and 20 more will achieve functional independence (defined as a mRS < 2). (10)

Nevertheless, several limitations have emerged concerning the methodological background of the HERMES trial, including the fact that all the data from this study come from high-volume comprehensive stroke centres with the highest expertise in endovascular treatment of AIS in the world.

In order to confirm a broad applicability of EVT into a real-world clinical practice and to establish the treatment effect of EVT at a national level, we compared the available neurothrombectomy data from the Czech Republic (CR) prospectively collected in the Safe Implementation of Treatments in Stroke – Thrombectomy (SITS-TBY) registry with data from the HERMES meta-analysis. We hypothesised that the safety and effectiveness of EVT in real-world clinical practice at a nationwide level are comparable with the results of the randomized control trials.

Methods

Nationwide data from the CR for the year 2016 were collected from the SITS-TBY registry. SITS (Safe Implementation of Treatments in Stroke) is a non-profit, free to use, research-driven, independent, international collaboration founded in the Karolinska Institute in Sweden. SITS was set up as an initiative to provide safe implementation of stroke treatments in routine clinical practice. It offers a platform for collecting high quality stroke data in over 1600 stroke centres. The registry is internet-based, which allows rapid data entry and retrieval and allows centres to compare their own treatment results on both a national and global scale. Data concerning patients with pre-treatment mRS scores of less than 2 and occlusions in the ICA and/or MCA treated with second-generation neurothrombectomy devices ± IV tPA (if eligible) were compared with the data from HERMES meta-analysis.

Demographic details, vascular risk factors and NIHSS scores (range 0-42, with higher scores indicating severe stroke) were collected for each patient. There was no upper age limit. All patients underwent NCCT followed by CTA from the aortic arch to the vertex to document LVO. Treatment decisions were made in comprehensive stroke centres in accordance with the current European guidelines. (50)

Outcomes included: NIHSS score at 24 hours after stroke onset, median change in NIHSS score from baseline to 24 hours, parenchymal haematoma type 2 (PH 2) according to the SITS-MOST criteria (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) and achievement of a mRS score of 0-2 at 90 days after stroke onset. Technical efficacy was assessed by counting the number of cases where a mTICI scale score of 2b or 3 was achieved (corresponding to reperfusion of at least 50% of the affected vascular territory). Reported times included: onset to reperfusion time, onset to groin time and groin to reperfusion time.

Ethics approval was obtained from the local institutional review boards and written informed consent was obtained from all patients.

Statistical analysis

Categorical variables are presented as absolute values and percentages, and continuous variables as mean and SD if symmetrically distributed, or otherwise as median and IQR. We used the Mann-Whitney test to compare continuous and ordinal variables because we did not have access to the raw HERMES data. We used the Chi-squared test to compare categorical variables. In order to determine whether it was possible to use the above-mentioned tests and that the effects were not due to chance alone we first calculated the intra-cluster correlation coefficient (ICC) for data of each centre by using Proc Mixed. All the tests were two-sided and significance was defined as a p-value of 0.05. Statistical analyses were obtained using SAS 9.3 software (SAS Institute, Cary, NC).

Results

Fourteen out of the 15 comprehensive stroke centres in the CR in 2016 reported data to the SITS-TBY registry. In this year 1,053 EVTs were performed in the CR. The smallest number of procedures performed by one centre was 17 and the largest was 136. Three centres performed more than 100 procedures, six centres performed between 50 and 100 procedures and six performed under 50 procedures per year (17, 34, 34, 34, 43, and 46). (51) Eight hundred and forty-five patients were reported to the registry. Incompleteness of data and/or patients who did not meet inclusion criteria led to exclusion of 241 patients. Therefore, the final dataset consisted of 604 (72%) of the total number of patients, representing 57% of all EVT cases performed in 2016 in the CR (with a pre-treatment mRS score of less than 2 and occlusion of the terminal ICA and/or MCA treated with second-generation neurothrombectomy devices ± IV tPA). Seventy per cent of these EVTs were mothership procedures and 30% were drip and ship procedures. CR and HERMES patients were comparable in age, sex, and baseline NIHSS. More CR patients were hypertensive and had diabetes mellitus and fewer patients were smokers. Fewer patients in the SITS-TBY cohort were treated with IV tPA: 76% vs. 83% (p=0.003). Occlusion locations were as follows (CR vs. HERMES): terminal ICA 22% vs. 21% (p=0.16), M1 MCA 62% vs. 69% (p=0.004), M2 MCA 16% vs. 8% (p<0.0001). The median times from onset to reperfusion were comparable: 232 vs. 285 minutes (p=0.66); the median groin-to-reperfusion times were 58 vs. 63 minutes.

Modified TICI 2b/3 was achieved in 74% (433/584) vs. 71% (390/549) of patients, OR 1.17 (95% CI=0.90-1.51), p=0.24. CR and HERMES patients did not differ in the median change in NIHSS score from baseline to 24 hours. There was no difference in percentage of PH 2 (5.7 vs. 5.1%), OR 1.12 (95% CI=0.66-1.90), p=0.68. A modified Rankin scale score of 0-2 at 3 months was achieved in 48% (184/268) vs. 46% (291/633) of patients, OR 0.92 (95% CI =0.71-1.18), p=0.48; **Figure 9**. The ICC for the mRS scores was estimated to be 0.023 and the ICC for NIHSS at 24 hours was 0.058, indicating only negligible differences among the centres.

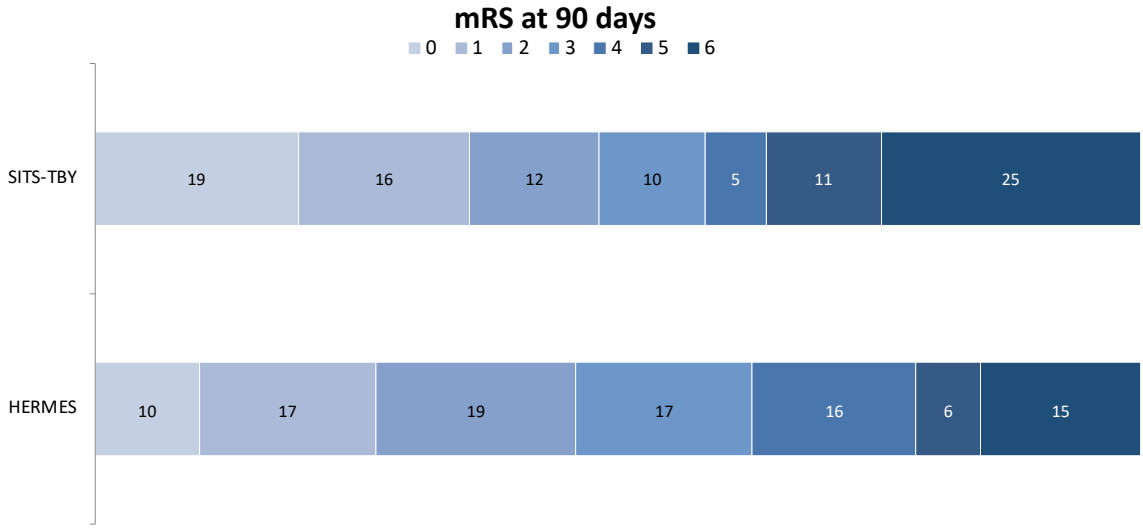
Table 7: Comparison of Czech SITS-TBY and HERMES data on demographic characteristics, past medical history, clinical and radiological characteristics, treatment details and outcomes

Demographic characteristics	**Czech Republic cohort (n=604)**	**HERMES (n=634)**	***p***
Median age, years	71 (63-79)	68 (57-77)	0.44
Sex, women	307 (51%)	304 (48%)	0.32
Past medical history			
Hypertension	442 (73%)	352 (56%)	<0.0001
Diabetes mellitus	159 (26%)	82 (13%)	<0.0001
Atrial fibrillation	209 (35%)	209 (33%)	0.56
Smoking (recent or current)	90 (15%)	194 (31%)	<0.0001
Clinical characteristics			
Baseline NIHSS score	15 (11-18)	17 (14-20)	0.66
Imaging characteristics			
ASPECTS on baseline CT	not available	9 (7-10)	-
Intracranial clot location:			
Terminal internal carotid artery	136 (22%)	122 (19%)	0.16
M1 segment middle cerebral artery	372 (62%)	439 (69%)	0.004
M2 segment middle cerebral artery	97 (16%)	51 (8%)	<0.0001
Extracranial ICA (tandem lesions)	55 (10%)	61 (10%)	0.987

Treatment details and procedural times (min)			
Treatment with intravenous alteplase	460 (76%)	526 (83%)	0.003
Onset-to-reperfusion time	232 (152-320); 467 patients	285 (210-362)	0.66
Onset-to-groin time	175 (100-767); 426 patients	238 (180-302)	0.66
Groin-to-reperfusion time	58 (44-208); 463 patients	63	-
Outcomes and safety:			
Modified TICI 2b/3	433/584 (74%)	390/549 (71%)	0.24
NIHSS at 24 hours	8 (4-17)	10.4 (8.7)	-
Median change in NIHSS score from baseline to 24 h	-5(-10 to 0)	-7 (-12 to -1)	0.66
Parenchymal haematoma type 2	5.7% (26/460)	5.1% (32/629)	0.68
mRS 0-2 after 3 months	48% (184/382)	46% (291/633)	0.48

Legend: Data are median (IQR), n (%), or mean (SD). NIHSS = National Institutes of Health Stroke Scale. ASPECTS = Alberta Stroke Program Early CT Score. ICA = internal carotid artery. mTICI = modified Thrombolysis in Cerebral Infarction Score. mRS = modified Rankin scale.

Figure 9: Modified Rankin Scale scores at 90 days



Legend: Distribution of scores at 90 days in per cents for the SITS-TBY and HERMES groups.

Discussion

Our analysis of the available national data on mechanical thrombectomy from the SITS-TBY registry confirms the applicability of neurothrombectomy in the real-world clinical practice.

As two thirds of the patients from the SITS-TBY registry had complete data, our analysis provides a relatively accurate population-based snapshot of the efficacy of EVT, comparable to the randomized control trials and previously published real-world thrombectomy experiences. STRATIS, the largest prospective multicenter (55 US centers) non-randomized registry including patients undergoing EVT with the Solitaire device, demonstrated that this procedure can be safely and efficaciously performed in the community setting. (52) Before the revelation of the STRATIS results, published data concerning EVT was limited, arising from mostly single-center studies with relatively low numbers of patients. (53) (54) One of the strengths of our study is that we included nationwide patient data from 14 comprehensive stroke centers from the year 2016, thus after the publication of the randomized control trials.

A total of 1,053 EVTs with second-generation neurothrombectomy devices were performed in the CR in 2016. If we take into the account the estimated incidence of acute ischemic stroke in the CR (211 per 100,000 inhabitants according to a recent stroke epidemiology survey) then approximately 5% of all acute ischemic stroke patients were treated with EVT in 2016. (55) This relatively high proportion of thrombectomy patients is consistent with previously reported data on EVT eligibility, reflecting the high level of organization of acute stroke care in the CR. (56) (57) (58)

The Institute for Health Information and Statistics of the CR has been collecting medical information for all patients admitted to all hospitals since 1992. All medical facilities are required by law to register all admissions and discharges and according to the Guidelines of the Czech Stroke Society, every patient with a diagnosis of stroke should be hospitalized and receive appropriate care in a specialized stroke unit. Since September 2016 the Czech Stroke Society have been monitoring EVTs performed in the CR. Every three months they report data on the number of EVTs performed per month and per center, the percentage of door-to-needle times under 30 min in IVT eligible patients, and procedural times, including median onset-to-groin time, median door-

to-groin time and median groin-to-reperfusion. Summary data reports including the parameters mentioned above are sent to all stroke centers and physicians involved in stroke care (neurologists and interventional radiologists). This serves as an important tool for improving acute stroke care logistics and reducing procedural times.

Randomized trials have demonstrated that workflow speeds are strongly associated with better functional outcomes, thus the reduction of procedural times should be targeted in every-day clinical practice. (59) (60) (61) Available onset-to-reperfusion and onset-to-groin times in our analysis (467 and 426 patients, respectively) are consistent with the HERMES meta-analysis, suggesting a good pre-hospital and in-hospital management of EVT candidates across the CR.

A robust predictor of functional outcome is successful reperfusion, defined as achievement of mTICI score of 2b or 3. Among the 549 HERMES patients who underwent EVT intervention and had mTICI scores documented, substantial reperfusion was achieved in 390 (71%) patients, which is consistent with our data; 433 out of 584 patients had mTICI scores of 2b or 3 (74%). In terms of the effect on improvement of neurological status, comparable the median change in NIHSS from baseline to 24 hours achieved in the Czech cohort was similar to the HERMES cohort, indicating a comparable clinical effect even in the non-randomized registry. In terms of safety, the proportion of patients with symptomatic PH type 2 was also similar (5.7 vs. 5.1%). Modified Rankin scale scores at 3 months as a marker of long-term disability was available in only 60% of our patients. The proportion of available patients with a good clinical outcome (mRS scores of 0-2) was comparable (48 vs. 46%). Nevertheless, it is important to be aware of the proportion of missing long-term outcome data. On the other hand, comparable short-term outcomes mentioned above (NIHSS scores at 24 hours and median change in NIHSS from baseline to 24 hours) indicate a positive effect of the procedure on early neurological recovery.

Although cerebral and vascular imaging is done in all IVT and EVT eligible patients in the CR before treatment decision making, ASPECT scores are not available in the SITS-TBY registry. (51) There are only two randomized controlled trials on mechanical thrombectomy in acute stroke published in which baseline cerebral imaging data were not used to select patients on the basis of the size of ischemic territory as determined by ASPECTS (THRACE

and MR CLEAN). (48) (62) According to the current European guidelines and results of our questionnaire survey run in January 2017, we can estimate that a majority of patients treated with EVT in the CR in 2016 had ASPECTS > 5 and were treated within 8 hours from stroke onset. (50) (51)

From demographic standpoint, HERMES and Czech SITS-TBY cohorts were balanced in age, sex and history of atrial fibrillation (**Table 7**). The groups differed in proportion of hypertensive, diabetic and smoking patients. Patients were comparable in the severity of admission neurological deficit assessed by NIHSS (moderate to severe stroke). HERMES and Czech SITS-TBY populations differed in clot locations in the M1 and M2 segments of the MCA as assessed by local radiologists and referred to the SITS-TBY registry, indicating that more interventions occurred for distal occlusions. Nevertheless, it is important to consider a challenge associated with a relatively poor standardization in distinguishing between the M1 and M2 MCA segments rated by different radiologists in our non-randomized analysis without a core lab rating of clot locations. This limitation of M1/M2 misclassification has been discussed in HERMES and elsewhere. (10) (63)

Our study has several limitations. We are aware that our comparisons with the clinical trials mentioned above are merely qualitative, since our data are based on a retrospective analysis of prospective registry data. As mTICI scoring was performed by the same attending interventionalist, who performed the procedure, and as clinical evaluation of disability (NIHSS and mRS) was not completely blinded, there may be a source of bias. Additionally, there are no imaging data stored in the SITS-TBY registry for neuroimaging core lab re-assessment, thus the possibility for misclassification of M1/M2 segments of MCA on CTA as discussed above or mTICI on final run digital subtraction angiography exists and limits our analysis. Another limitation is missing long-term outcome data in the SITS-TBY registry.

Section 3.2 – Thrombectomy vs. Medical Management in Low NIHSS Acute Anterior Circulation Stroke

Based upon: VOLNY, Ondrej, Charlotte ZERNA, Ales TOMEK, Michal BAR, Miloslav ROCEK, Radek PADR, Filip CIHLAR, Miroslava NEVSIMALOVA, Lubomir JURAK, Roman HAVLICEK, Martin KOVAR, Petr SEVCIK, Vladimir ROHAN, Jan FIKSA, David CERNIK, Rene JURA, Daniel VACLAVIK, Petra CIMFLOVA, Josep PUIG, Dar DOWLATSHAHI, Alexander V. KHAW, Enrico FAINARDI, Mohamed NAJM, Andrew M. DEMCHUK, Bijoy K. MENON, Robert MIKULIK a Michael D. HILL. Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. *Neurology* [online]. 2020.

Abstract

Background – EVT is highly effective for acute ischemic stroke with LVO and moderate to severe neurological deficits.

Objective: To undertake an effectiveness and safety analysis of EVT in patients with LVO and NIHSS≤6 using datasets of multicentre and multinational nature.

Methods – We pooled patients with anterior circulation occlusion from three prospective international cohorts. Patients were eligible if presentation occurred within 12 hours from last known well and baseline NIHSS≤6. Primary outcome was mRS 0–1 at 90 days. Secondary outcomes included neurological deterioration at 24 hours (change in NIHSS of ≥ 2 points), mRS 0-2 at 90-days and 90-day all-cause mortality. We used propensity score matching to adjust for non-randomized treatment allocation.

Results – Among 236 patients who fit inclusion criteria, 139 received EVT and 97 received medical management. Compared to medical management, the EVT group was younger (65 versus 72 years; p<0.001), had more proximal occlusions (p<0.001), and less frequently received concurrent IVT (57.7% versus 71.2%; p=0.04). After propensity score matching, clinical outcomes between the two groups were not significantly different. EVT patients had an 8.6% (95% CI: -8.8–26.1%) higher rate of excellent 90-day outcome, despite a 22.3% (95% CI: 3.0–41.6%) higher risk of neurological deterioration at 24 hours.

Conclusions – EVT for LVO in patients with low NIHSS was associated with increased risk of neurological deterioration at 24 hours. However, both EVT and medical management resulted in similar proportions of excellent clinical outcomes at 90 days.

Introduction

Patients with AIS due to LVO usually suffer from severely disabling symptoms. (64) However, a significant number of LVO patients present with milder symptoms. (65) EVT is a standard of care for AIS due to LVO, but level 1A guideline recommendations for EVT are currently restricted to LVO patients with NIHSS ≥ 6, since only a limited number of patients with low baseline NIHSS was enrolled in the randomized controlled trials. (9) (10)

AIS with NIHSS ≤ 6 is routinely considered as "mild" and "non-disabling". However, one in four LVO patients with low baseline NIHSS suffer early neurologic deterioration resulting in poorer outcome. (66) (67) (68) From a patient perspective, milder deficits can restrict daily activities and can be devastating to their quality of life. Patients with LVO and low baseline NIHSS often have distinct clinical, demographic, and hospital arrival characteristics. (69) Multiple non-randomized studies have sought to evaluate the efficacy and safety of EVT in such patients and showed mixed results. These studies were mostly limited by their non-randomized design, small sample size, single-center experiences, varying practice or including patients treated prior to the efficacy of EVT was proven and incorporated into the (inter)national guidelines. (69) (70) (71) (72, 73) (74) (75) (76)

The aim of our observational multicentre study was to assess the effectiveness and safety of EVT versus medical management in patients with LVO and NIHSS ≤ 6 using recent data from comprehensive datasets and propensity score matching.

Methods

The data that support the findings of this study are available from the corresponding authors upon reasonable request. We retrospectively identified acute stroke patients with CTA proven anterior circulation occlusion and admission NIHSS ≤ 6. For this purpose, we retrieved EVT data from the Safe Implementation of Treatments in Stroke–Thrombectomy registry (SITS-TBY) and compared them with medical management data derived from the INTERRSeCT and PROVE-IT study.

Standard Protocol Approvals, Registrations, and Patient Consents

Permissions to analyze data for the SITS-TBY (a non-profit, quality improvement-driven, international) registry were provided by the ethics committee of St. Anne's University Hospital, Brno, Czech Republic; individual patient consent for the SITS-TBY registry was not sought. The PROVE-IT study used a waiver of consent which was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Written informed consent was provided by the patient or a surrogate for the INTERSeCT study. The reviews of the Institutional Review Boards (IRB) for each study determined that informed consent was not required for this current pooled analysis. The study protocol was approved by the scientific committees of each study.

Endovascular data source

National EVT data from the CR were extracted from the population-based SITS-TBY registry from January 2015 to December 2018 to cover the time period after the publication of positive endovascular trials. The SITS-TBY registry represents a non-profit, research-driven, international registry collecting data on endovascular treatment. Anonymized patient-level data are entered at each stroke center either by a research nurse or physician at discharge or at 90-days follow-up. There has been no formal audit of the Czech SITS-TBY or global SITS-TBY data. However, 12 (out of 15) comprehensive stroke centers participated in the registry in 2016 as part of a quality improvement program. Random hospital-level metrics reported to the Czech Ministry of Health were cross-checked with the SITS data and showed high level of consistency (unpublished). Additionally, a nationwide questionnaire survey run in 2016 did not show major differences in clinical practise including neuroimaging, logistics and treatment standards in all 15 comprehensive stroke centers in the CR, for details see

ANNEX 4). Furthermore, since 2016, the Czech Stroke Society has been providing feedback quarterly to all participating stroke centers on number of EVT cases and time metrics based on the data from the registry. Patients for endovascular treatment in the CR are selected through CT and CTA imaging.

Medical management data source

Medical management was based on the current guidelines (Canadian Stroke Best Practise Recommendations), American Heart and Stroke Association), including IVT in patients presenting within the first 4.5 hours from last seen normal. In patients not eligible for IVT, an antiplatelet agent was administered on day 1, unless there was an indication for early anticoagulation.

The two non-thrombectomy cohorts were selected from the multicentre international observational studies: 1) Measuring Collaterals with Multi-phase CT Angiography in patients with Ischemic Stroke (PROVE-IT, patient enrolment between July 2014 to October 2017); and 2) Identifying New Approaches to Optimise Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography study (INTERRSeCT, patient enrolment between March 2010 to March 2016).

PROVE-IT was a prospective multi-center cohort study of 500 consecutive patients with AIS presenting within 12 hours of stroke symptom onset with evidence of intracranial occlusion on routine CTA. The primary aim of this trial was to evaluate imaging selection for thrombolysis and EVT decision-making in the setting of AIS. (77) INTERRSeCT was a multicentre prospective cohort study that enrolled 575 patients with AIS with intracranial thrombi documented via CTA. The study included patients with a wide range of clinical presentations (within 12 hours from last known well), occlusion sites, and thrombus characteristics to identify clinical and imaging variables associated with recanalization with or without IVT. (78)

For the current study, we only included patients who were independently functioning in the community immediately prior to their stroke (estimated baseline mRS 0-2). Patients

were further eligible if they presented to the emergency department with symptoms consistent with AIS 12 hours from time last known well, baseline NIHSS≤6, and baseline CTA with the evidence of symptomatic intracranial occlusion (ICA or MCA including M1 and proximal M2 segments). Patients with the primary posterior circulation occlusions were excluded.

Demographics, Variables, and Measurements

Information on baseline demographics, vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, smoking history (current/past), congestive heart failure), time last seen normal, NIHSS score (range, 0-42, with higher scores indicating severe stroke), occlusion location (ICA, M1, M2 MCA), prior use of anticoagulation, prior use of antithrombotic treatment, intravenous alteplase administration (if applicable although many low NIHSS patients are not thrombolysed), were collected. Other clinical endpoints were 24-h NIHSS and functional outcome at 90 days measured on the mRS.

Study outcomes

Modified Rankin Scale 0–1 at 90 days was chosen as the primary outcome because patients with mild deficits at baseline are more likely to have excellent outcomes. Secondary outcomes were the neurological deterioration at 24 hours (defined as increase of NIHSS score by 2 or more points)(79), mRS 0-2 at 90 days and all-cause mortality at 90 days.

Missing/incomplete data

Among 236 patients, four had missing baseline NIHSS, five missing prior anticoagulation history, six missing prior smoking history, six prior atrial fibrillation history, one missing prior hypertension and prior dyslipidemia history; 14 missing 24-h NIHSS, 13 missing 90-days mRS. We imputed the missing NIHSS baseline values with the group median from the remaining available data and imputed "no" for missing binary variables. The 13 missing values for 90-day mRS were again imputed with the median of the remaining available data. Since all missing mRS occurred in the EVT group, we performed additional sensitivity analysis assuming that the missing 90-day mRS values indicated that the person did not reach a favorable outcome and was disabled/dead (i.e. worst-case scenario), did achieve a favorable outcome (i.e. best-case scenario), and omitted cases with missing mRS

scores. For the 14 missing values of 24h-NIHSS (all but one from the EVT group) we assumed that the patients had neurological deterioration (i.e. worst-case scenario).

Data about intracranial hemorrhages were missing and unverifiable in the SITS-TBY registry and could thus not be analyzed in our current study. Since the SITS-TBY registry is a study of implementation of thrombectomy in routine clinical practice, it was not mandated that time metrics were being collected. Onset-to-treatment times were thus not available for our analysis.

Statistical analysis

Standard descriptive statistics were used to measure central tendency and variability of baseline characteristics. Ordinal/continuous variables were compared by the Mann-Whitney test or t-test based on their distribution. Categorical variables were compared using the Fisher's exact test. Since our data were not randomized, we used propensity score matching to estimate the adjusted treatment effect of EVT compared to the best medical management, accounting for differences in baseline variables. We used the treatment effect option with propensity score matching in STATA version 14.2 (College Station, TX). Derivation of standard error accounted for the fact that propensity scores are estimated rather than known. Propensity scores were derived from a multivariable logistic regression model that calculates the treatment probability for each subject. This model was adjusted for the following clinically relevant baseline variables: sex, age, occlusion location, thrombolysis status, baseline mRS, prior antithrombotic treatment and NIHSS. The propensity scores were then used to impute the missing potential outcome (if a subject received EVT then medical management is considered counterfactual and if the subject received medical management then EVT is considered counterfactual) for each subject by taking the outcome of a similar subject that received the other treatment level (or multiple subjects if there was a tie for similarity). Similarity between subjects was based on the propensity scores. Common support was assessed using an overlap plot and examination of mean propensity scores by treatment group and quintiles and found to be adequate (**Table 8**). The treatment effect was computed by taking the average of the difference amongst each EVT and medical management pairs, where outcomes were either observed or derived as the counterfactual from the propensity matching process and presented as a risk difference with 95% confidence interval (CI). We used this method of matching and analysis for our primary, secondary and safety

outcomes. We visualized the unadjusted data and the results of our primary analysis using horizontally stacked bar graphs. Sensitivity analysis was performed for the primary outcome using the worst-case scenario, best-case scenario and by omitting cases with missing primary outcome as described above. All tests were two-sided and the significance level was considered as 0.05. Statistical analyses were performed using STATA version 14.2 (College Station, TX).

Results

Baseline Characteristics

Our pooled dataset resulted in 281 patients with LVO and mild symptoms. We excluded eleven patients who were not independent at baseline, 33 patients with distal M2, M3 and no occlusion, and one patient treated with tenecteplase (TNK). This left 236 patients for analysis; 139 received EVT and 97 medical management. The two groups had similar baseline NIHSS, baseline mRS and baseline vascular risk factors. The EVT group was younger (65 versus 72 years), with more proximal occlusions (50.4% M1 and 15.8% ICA versus 25.8% M1 and 2.1 ICA), and less concurrent intravenous alteplase treatment (57.7% versus 71.2%) as illustrated in **Table 9**.

Primary and secondary outcomes

Ninety-day excellent outcome (mRS 0-1) was achieved in 62.7% (n=148) of patients overall, with no difference between the EVT and medical management group (61.9 % versus 63.9 %, p=0.785) in unadjusted analysis. The raw distribution of mRS scores between the EVT and medical management group at 90 days is shown in **Figure 10**. After propensity score matching, patients in the EVT group had an 8.6% (95% CI: -8.8% – 26.1%) higher chance of excellent outcome at 90 days compared to the medical management group. The distribution of mRS scores of the EVT and medical management group at 90 days after the propensity score matching is presented in **Figure 11**. The result was unchanged in sensitivity analysis using the worst-case scenario (missing outcomes assumed to have achieved mRS 2-6) and when cases with missing mRS were omitted (p=0.33 and p=0.250, respectively). However, assuming best-case scenario (missing outcomes actually achieved mRS 0-1), patients in the EVT group had a 17.6% (95% CI: 0.01% – 35.4%) higher chance of excellent outcome at 90 days compared to the medical management group.

Unadjusted analyses of the secondary outcomes are shown in **Table 10**. After propensity score matching, patients in the EVT group had a 22.3% (95% CI: 3.0% – 41.6%) higher risk of neurological deterioration at 24 hours compared to patients in the medical management group. Patients in the EVT group also had a 2.2% (95% CI: -3.6% - 7.9%) higher risk of death from any cause within the first 90 days after the index event compared to the medical management group.

Table 8: Mean Propensity Scores by Quintiles and Treatment Group

	Propensity Score Quintile	No. of observations	Mean Propensity Score
Medical management	1	16	0.149
	2	32	0.324
	3	32	0.505
	4	11	0.702
	5	6	0.903
Thrombectomy	1	-	-
	2	15	0.316
	3	34	0.508
	4	37	0.711
	5	53	0.915

Table 9: Baseline Characteristics before Propensity Score Matching Process

Variable	Medical Management group N = 97	Endovascular group N =139
Median age in years (25% – 75%)	72 (63 – 80)	65 (55 – 75)
Sex, male, %	48.9	43.4
Occlusion site, %		
Internal carotid artery	2.1	15.8
Tandem occlusion	2.1	3.6
M1 segment	25.8	50.4
Proximal M2 segment	70	30.2
Median baseline NIHSS (25% – 75%)	5 (4 – 6)	4 (3 – 6)
Baseline modified Rankin Scale, %		
0	87.6	87.8
1	7.2	5.0
2	5.2	7.2
Intravenous alteplase treatment, %	71.2	57.7
Prior anticoagulation, %	9.4	10.3
Prior antithrombotic treatment, %	25.2	44.3

Hypertension, %	65.5	68
Diabetes mellitus, %	14.4	10.8
Dyslipidemia, %	26.6	38
Atrial fibrillation, %	23.7	28.9
Smoking current/past, %	28.9	22.3
Ischemic heart disease, %	6.5	3.1

Legend: NIHSS means National Institutes of Health Stroke Scale

Table 10: Unadjusted Outcome Analysis

Outcome	Medical Management group N = 97	Endovascular group N =139	Fisher's exact test, p-value
modified Rankin Scale score 0-1 at 90 days, %	63.9	61.9	0.785
Neurological deterioration at 24 hours, %	10.3	30.2	<0.001
modified Rankin Scale score 0-2 at 90 days, %	79.4	69.1	0.100
All-cause mortality at 90 days, %	3.1	5.0	0.532

Figure 10: Unadjusted analysis of 90-day modified Rankin Scale shift

Legend: EVT means endovascular treatment, MM medical management, mRS modified Rankin scale.

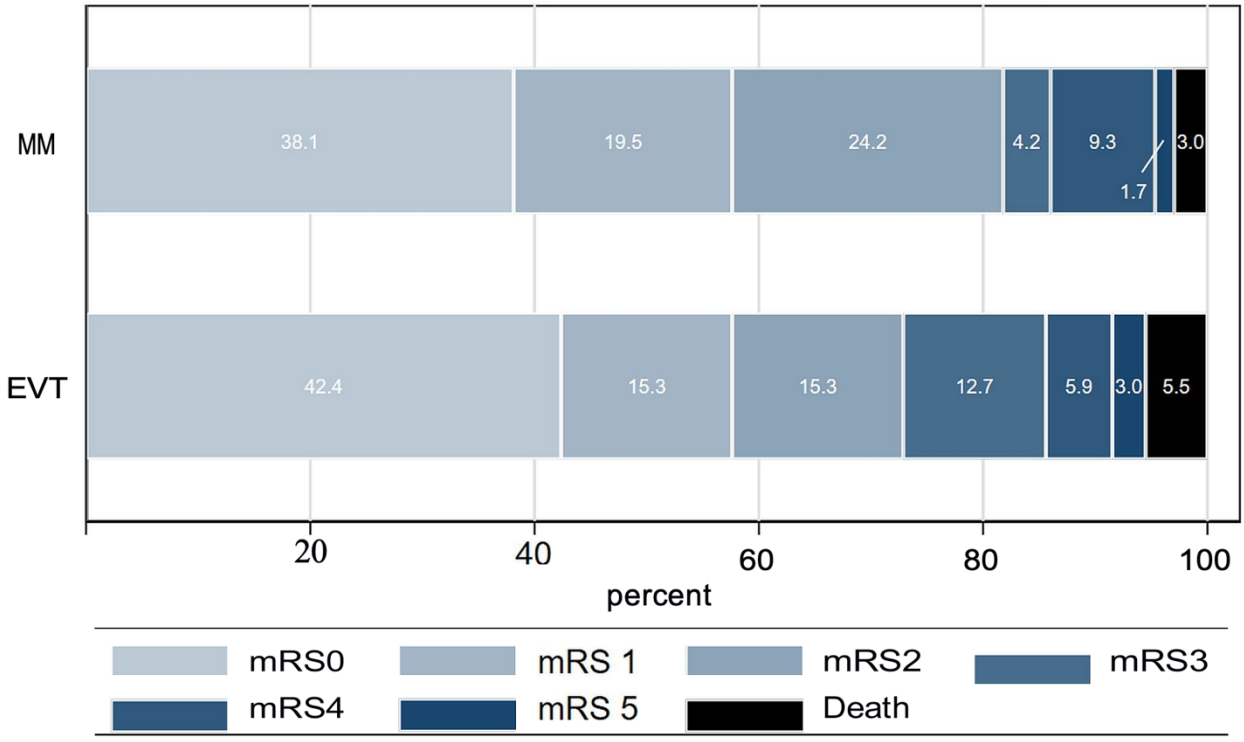
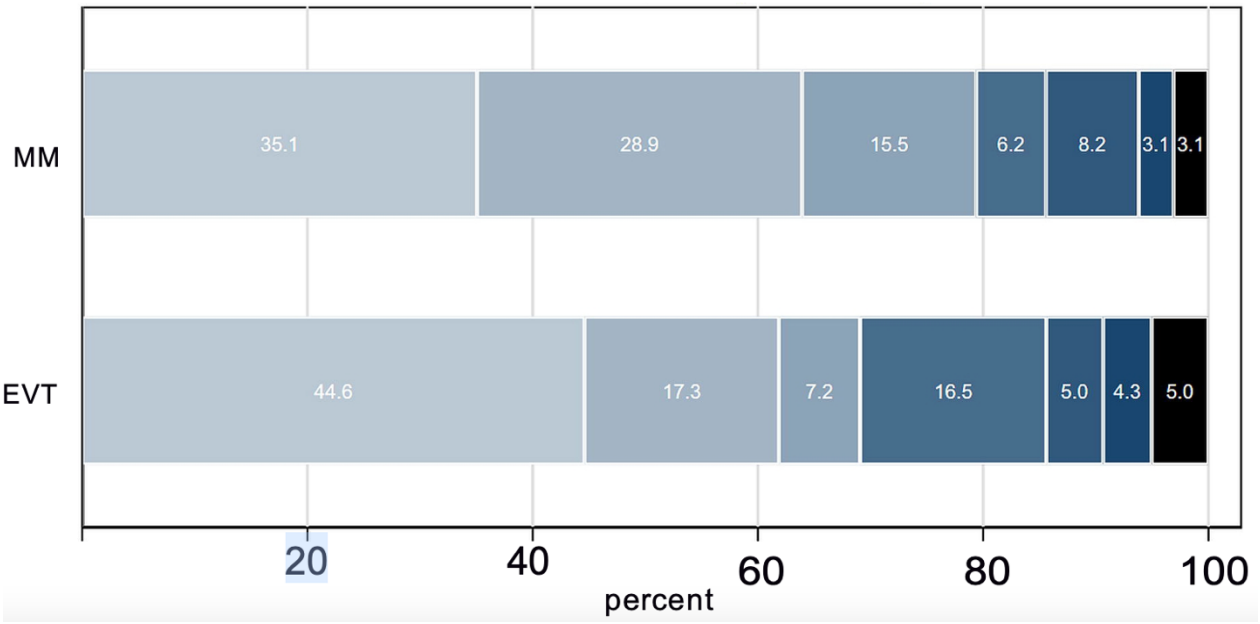


Figure 11: Propensity-Score matched analysis of 90-day modified Rankin Scale shift

Legend: EVT means endovascular treatment, MM medical management, mRS modified Rankin Scale.



Discussion

In our study endovascular treatment and best medical management for large vessel anterior circulation occlusion in patients presenting with low NIHSS resulted in similar proportions of excellent functional outcome at 90 days and comparable all-cause 90-day mortality. This outcome parity occurred despite an increased endovascular treatment risk of neurological deterioration at 24 hours.

In keeping with our results, other smaller multicenter studies have utilized propensity score matching and found no significant difference in the excellent functional outcome at 90-days. (70) Although the study by Nagel *et al* (77 matched pairs) showed a 14.4% absolute difference in good clinical outcome (84.4% versus 70.1%, p=0.03) defined as mRS 0-2 and an adjusted OR of 3.1 (95% CI, 1.4-6.9) favoring immediate EVT, there was no such difference seen for excellent outcome defined as mRS 0-1 at 90 days. (71) Additionally, the study enrolled 7% of patients with basilar occlusions and 6% of patients with initial mRS>2 (20/300 patients). In the study by Haussen *et al*, the protocol also allowed inclusion of patients with basilar occlusions, which then made up 23% of the EVT group. (73) These and other previously published (mostly single-center) studies have selected individual sites with variability in their approach to patient care and differing local treatment guidelines. A more recent study by Asdaghi *et al* looked at over 400 registry patients and found association of EVT with favorable discharge outcomes and ambulatory status. (69) However, the 90-day outcomes as well as the occlusion status and thrombus location were not documented consistently. All of the above mentioned studies included patients who received EVT before the publication of positive randomized control trials in 2015 and thus the incorporation of EVT as a standard of care into national guidelines. Thus, the results of these studies might be reflective of the heterogeneity in workflow and experience with such patients and might not be representative of the current clinical practice.

We found no difference in all-cause 90-day mortality in our study, which is in congruence with the smaller multicentre studies of Nagel *et al* and Dargazanli *et al.* In the study of Sarraj *et al*, the patients undergoing EVT had higher mortality (8.9% versus 1.1%, p=0.03) possibly driven by increased risk of symptomatic ICH (5.8% versus 0%). Similarly, Asdaghi *et al* reported mortality of 5.2% and symptomatic ICH rates of 4.5%.

Endovascular treatment was associated with increased risk of neurological deterioration at 24 hours (defined as $\geq$ 2 points increase of the NIHSS scale) in our propensity-score matched analysis. One possible explanation might be the occurrence of symptomatic ICH with the endovascular treatment. Neurological deterioration might have also been more apparent on formal testing in a setting of mild initial symptoms and thus been more diligently scored. Further, other complications of EVT including embolic events into other arterial territories, arterial access adverse events such as haemorrhage, retroperitoneal hematoma and pseudoaneurysm formation may impact 24-hour assessment.

Multiple studies have shown that since low NIHSS patients are generally considered too mild for thrombolysis and EVT, up to one third end up disabled or dead at the 90-day follow-up when left hyperacutely untreated. (80) (81) (82) (83) It is known that in stroke due to (large) vessel occlusion, there is a clear relationship between recanalization and favorable/excellent outcome even though our current study and various other have shown differing effect sizes (from 8.6% to 14.4%). (71) (84) Yet, interventional treatment, whether medical with IVT or interventional with endovascular thrombectomy has possible harm. The value of a future randomized controlled trial in this patient cohort is thus not to show the benefit of EVT but rather to assess if the benefit outweighs the potential harm of the treatment. Data about intracranial hemorrhages were missing and unverifiable in the SITS-TBY registry and could thus not be analyzed in our current study. But two previous studies in low NIHSS strokes that have specifically measured sICH found a notable difference between the EVT and medical management group (Sarraj *et al* 5.8% vs. 0% [p=0.02], Nagel *et al* 5% vs. 1.4% [p=0.08]). (70) (71) However, these are sICH risks that we accept for moderate-severely disabling stroke and the acceptable risk of sICH must be significantly less in low NIHSS strokes to justify the risk of death and disability as a complication of EVT. Due to this uncertainty in numbers, despite several analyses from groups around the world, a well-designed randomized controlled trial would be able to finally answer the question about the risk-benefit-ratio of EVT for low NIHSS strokes.

The strength of our study is its multicenter and multinational nature of the utilized datasets. The national population-based EVT data were extracted from the SITS-TBY registry

from January 2015 to December 2018 in order to cover the time period after the publication of positive endovascular trials and as such reflect the current clinical practice.

Our study is limited by its retrospective nature and even though we tried to account for confounding by using advanced statistical methods, there is still a risk of residual confounding due to unmeasured variables. For example, even though we incorporated occlusion location into our propensity score model, we were unable to also incorporate a measure of early ischemic changes since these data were not available in the SITS-TBY registry. Furthermore onset-to-treatment times were not available for our analysis. Although twelve of total 15 comprehensive stroke centers in the Czech Republic contributed to the SITS-TBY registry during the study period. Our previous study showed that over 80% of all EVT cases in the CR were reported to the registry in 2016. (85) We also had no data on the use of anesthesia/sedation during EVT available. Blood pressure changes during induction of general aneasthesia may risk penumbral tissue perfusion and might thus contribute to the neurological deterioration at 24 hours. (86) (87) The mRS, even though one of the most commonly used clinical outcome markers in stroke and captured by the three observational data sources we have used, lacks sensitivity at the minor disability end of the scale and we might thus have not been able to detect a significant difference in our primary outcome. Our matched analysis is larger than the sample size of prior studies but still might have affected our statistical power to detect a true difference.

Conclusions

The first study (Section 2.1) comparing the assessment of early ischemic changes by expert reading and available automated software for NCCT and CTP demonstrated high accuracy for the evaluation of early ischemic changes by different CT modalities. The best accuracy was found for the CBF<30% and Tmax>10s parameters. The use of automated software in daily clinical practice has a potential to improve detection and extent of early ischemic changes.

The second study (Section 2.2) focused on utility of time-variant multiphase CTA color maps brought new evidence that collateral extent assessed on the time-variant mCTA maps improved prediction of good clinical outcome and had similar utility in predicting follow-up infarct volume compared to conventional mCTA collateral grading as previously published.

The third study (Section 3.1) comparing EVT data from the Czech Republic with data from the HERMES meta-analysis confirmed the applicability of EVT in a nationwide real-world practice for a CTA proven LVOs in the anterior cerebral circulation.

Our multicenter observational post-hoc study (Section 3.2) showed that the EVT for LVO in patients with low baseline NIHSS resulted in similar 90-day clinical outcomes compared to the best medical management despite an increased odds of neurological deterioration at 24 hours.

List of Abbreviations

ACC – accuracy

AIC – acute ischemic stroke

ASPECTS – Alberta Stroke Program Early CT Score

AUC – area under the curve

BIC – Bayesian information criteria

CBF – cerebral blood flow

CBV – cerebral blood volume

CI – confidence interval

CT – computed tomography

CTA – computed tomography angiography

CTP – computed tomography perfusion

CR – Czech Republic

DWI-MRI – diffusion-weighted imaging – magnetic resonance imaging

EVT – endovascular treatment

HU – Hounsfield units

ICA – internal carotid artery

ICC – intra-cluster correlation coefficient

ICH – intracerebral haematoma

IQR – interquartile range

IVT – intravenous thrombolysis

LVO – large vessel occlusion

Ls-means – least square means

MCA – middle cerebral artery

mCTA – multiphase CTA

MIPs – maximum intensity projections

MT – mechanical thrombectomy

mTICI – modified Thrombolysis in Cerebral Infarction

MTT – mean transit time

mRS – modified Rankin Scale

NCCT – non-contrast CT

NIHSS – National Institutes of Health Stroke Scale

NPV – negative predictive value

OR – odds ratio

PH – parenchymal haematoma

PPV – positive predictive value

SD – standard deviation

SITS-MOST – Safe Implementation of Thrombolysis in Stroke-Monitoring Study

SITS-TBY – Safe Implementation of Treatments in Stroke – Thrombectomy registry

TICI – Thrombolysis in Cerebral Infarction

Tmax – time to maximum

TNK – tenecteplase

TNR – true negative value

tPA – tissue plasminogen activator

TPR – true positive value

WL – window level

WW – window width

List of Figures

List of Tables

Annex 1

VOLNY O., P. CIMFLOVA, T.-Y. LEE, B. K. MENON and C. D. D'ESTERRE. Permeability surface area product analysis in malignant brain edema prediction – A pilot study. Journal of the Neurological Sciences [online]. 2017, 376, 206–210. ISSN 0022-510X

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Permeability surface area product analysis in malignant brain edema prediction – A pilot study

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ABSTRACT

Background and purpose: Using an extended CT perfusion acquisition (150s), we sought to determine the association between perfusion parameters and malignant edema after ischemic stroke.

Methods: Patients (from prospective study PROVE-IT, NCT02184936) with terminal internal carotid artery ± proximal middle cerebral occlusion were involved. CTA was assessed for clot location and status of leptomeningeal collaterals. The following CTP parameters were calculated within the ischemic territory and contralaterally: permeability surface area product (PS), cerebral blood flow (CBF) and cerebral blood volume (CBV). PS was calculated using the adiabatic approximation to the Johnson and Wilson model. Outcome was evaluated by midline shift and infarction volume on follow-up imaging.

Results: Of 200 patients enrolled, 7 patients (3.5%) had midline shift ≥ 5 mm (2 excluded for poor-quality scans). Five patients with midline shift and 5 matched controls were analysed. There was no significant difference in mean PS, CBF and CBV within the ischemic territory between the two groups. A CBV threshold of 1.7 ml/100 g had the highest AUC = 0.72, 95% CI = 0.54–0.90 for early midline shift prediction, sensitivity and specificity were 0.83 and 0.67 respectively.

Conclusion: Our preliminary results did not show significant differences in permeability surface area analysis if analysed for complete ischemic region. CBV parameter had the highest accuracy and there was a trend for the mean PS values for midline shift prediction.

1. Introduction

The incidence of malignant brain edema in anterior circulation ischemic stroke ranges between 3 and 10%. Even with adequate reperfusion, this severe complication has high rates of morbidity and mortality [1]. In clinical practice, an acute predictor/s to identify patients who would benefit from early decompressive hemicraniectomy before a midline shift develops remains elusive [2,3].

Increased tissue water during ischemia is caused by the combination of cytotoxic edema and vasogenic edema. The former, which results in swelling of cells of the neurovascular unit, occurs within minutes of ischemia and is often less severe than the latter, which results in an increase in extracellular free water due to BBB breakdown, occurring hour to days after stroke onset [4,5]. Pathophysiologically, an early impairment of cerebrovascular autoregulation in peri-infarct tissue, loss of integrity of the endothelial basal lamina and increased vascular permeability play key roles in the development of massive life-threatening brain edema in acute ischemic stroke patients [6,7]. Several radiological markers for the development of malignant edema in anterior circulation strokes have been studied, including admission non-contrast computed tomography (CT) hypodensity extending 50% of the MCA territory or diffusion weighted imaging (DWI) lesion extending 82 ml or 145 ml, and ^{11}C-flumazenil positron emission tomography (FMZ-PET) [8–11].

There have been also several CT perfusion (CTP) studies that have attempted to find acute biomarkers predictive of malignant MCA edema [12–16]. Acute differences in cerebral blood flow, blood brain barrier (BBB) permeability and cerebrovascular reserve did not correlate with malignant edema; however, these studies were hampered by limited CTP acquisition lengths, which are especially important for calculation of permeability surface area (PSA) as a marker of BBB disruption. Therefore, our study used multiple imaging modalities (multiphase CTA and an extended length CTP scanning protocol) along with several clinical variables from the prospective study PROVE-IT [Precise and Rapid assessment of collaterals using multi-phase CT angiography

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0022-510X/

in the triage of patients with acute ischemic stroke for intravenous (IV) tPA or intra-arterial therapy (IAT)] to determine their relationship with the development malignant brain edema.

2. Methods

2.1. Patients

The preliminary analysis included first 200 patients from the PROVE-IT study (registered at ClinicalTrials.gov under the registration number NCT02184936) with proven terminal occlusion of the internal carotid artery (ICA) ± proximal occlusion of the middle cerebral artery (MCA). Patients with early midline shift ≥ 5 mm according to the control CT or MRI of the brain performed within 24–32 h were identified in the study group. They were subsequently matched with control patients (with no midline shift) who had a similar admission neurological deficit according to the National Institutes of Health Stroke Scale (NIHSS), comparable early ischemic changes assessed by Alberta Stroke Program Early CT Score (ASPECTS) and similar volume of infarction on the control imaging.

2.2. Imaging and image acquisition

Multiphase CT angiography (mCTA) and CTP (64-slice Lightspeed, GE Healthcare, Waukesha, WI, USA) were acquired within the scope of the study imaging protocol. Time-resolved cerebral angiograms of the brain vasculature were generated following the injection of 80 ml of contrast agent (Optiray® 320; Mallinckrodt Pharmaceuticals; Dublin, Ireland), injected at a rate of 5 ml/s followed by a saline flush of 50 ml at 6 ml/s. For the first phase, the aortic arch-to-vertex helical scan was timed to be in the peak arterial phase of normal brain by triggering the scan based on bolus tracking. This first phase acquisition was 7 s in length. The second phase was acquired after a delay of 4 s allowing for table repositioning to the skull base. Scan duration for each additional phase is 3.4 s. An advantage of mCTA is that it allows dynamic imaging of cerebral circulation and a detailed view of the leptomeningeal collaterals. For the CTP acquisition, 45 ml of CT contrast agent (Optiray® 320; Mallinckrodt Pharmaceuticals; Dublin, Ireland) was power injected at 4.5 ml/s followed by a saline flush of 40 ml at 6 ml/s. Sections of 8 cm thickness were acquired at 5 mm slice thickness. Scanning began after a delay of 5 s from contrast injection in up to two phases (scanning intervals): 1st phase every 2.8 s for 60 s (in 30 patients) and an additional 2nd phase every 15 s for 90 s (in 47 patients).

2.3. Image analysis

All imaging data were analysed at the imaging core lab of the Calgary Stroke Program (Canada). OsiriX version 3.5 (http://www.osirix-viewer.com). Leptomeningeal collaterals were assessed on baseline multiphase CTA by a consensus (O.V., P.C.) [17]. The CTP parameters permeability surface area product (PS), CBF, CBV and time to maximum (T_{max}) were calculated using commercially available software with a delay-insensitive deconvolution algorithm (CT Perfusion 4D, GE Electric Healthcare, Waukesha, WI, USA).

A physiologically appropriate deconvolution-based distributed parameter model was used for the CTP analysis [18]. This method corrects for the inability to administer a contrast bolus directly into an artery supplying a tissue of interest. Following the injection of contrast into a peripheral vein, the bolus undergoes delay and dispersion prior to arriving at region of interest within the brain [19]. To correct for this, an impulse residue function (IRF), which represents the tissue time-attenuation curve (TAC) obtained under the ideal hemodynamic injection conditions is calculated – essentially, this removes the effect of delay/dispersion (Fig. 1). The IRF can be interpreted as the volume of blood flow entering a capillary network that contains a fraction of contrast medium that is instantly deposited into the tissue of interest as

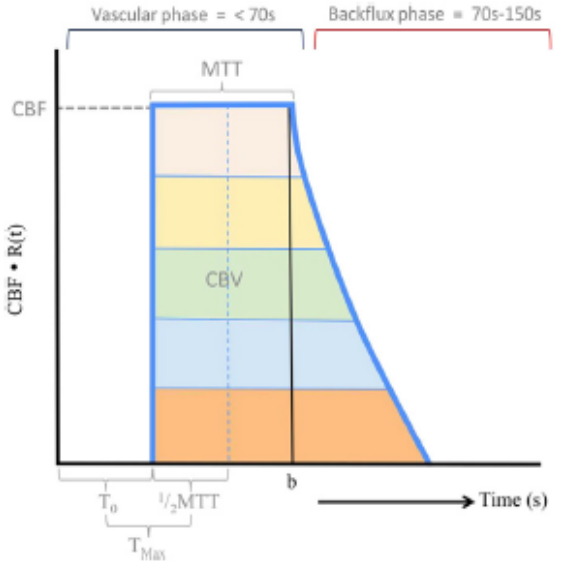

Fig. 1. Graphical representation of an ideal flow-scaled (CBF · $R(t)$) IRF. The IRF is obtained in the brain $R(t)$, using the deconvolution of the arterial enhancement curve $C_a(t)$ and tissue TAC $Q(t)$. The height of the IRF defines CBF, the area of the IRF represents the CBV, and "b" signifies the MTT, which is calculated as the area under the curve (CBV) divided by the height of the vertical line above "b" (CBV). T_0 is the time from the arrival of contrast at the AIF to the tissue of interest and adding $^1/_2$ MTT gives the time for the impulse residue $R(t)$ to reach its maximum (T_{max}). PS is calculated during the "backflux" phase.

time progresses and has been described previously for perfusion parameters, CBF, CBV, MTT and T_{max} [20,21].

PS of the BBB was calculated using the adiabatic approximation Johnson and Wilson model, which assumes that all contrast agent is distributed in either the capillaries or the extracellular space [18]. Contrast measured in the extracellular space is a surrogate of the degree of BBB compromise, which is correlated with quantitative measurements of PS [22]. This model can be illustrated as 1) a single cylinder of length (L) containing a specific blood volume (Vb) that represents the intravascular (capillary) space and 2) another cylinder that surrounds the capillary containing a volume (Ve) that represents the extravascular (interstitial) space (Fig. 2) [23]. A second assumption of this model comes from the fact that the capillary endothelium will have varying degrees of permeability and therefore a bidirectional movement of contrast between the two compartments [24]. To simplify things, it is also

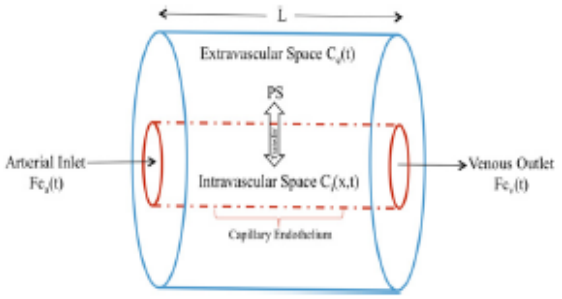

Fig. 2. A simplified diagram of the Johnson and Wilson model. The brain is divided into two principal compartments: the extravascular (interstitial) and intravascular space, separated by a permeable capillary endothelium. The concentration of contrast within the intravascular space is a function of time and length along the capillary, while the concentration of contrast in the extravascular space is assumed to be evenly distributed along the length of the capillary and is only a function of time. This model thereby describes the rate of change of contrast diffusion in the extravascular space, defined by the PS.

assumed that there is negligible radial contrast concentration gradient in the intravascular space and an even (quasi-steady state) distribution of contrast agent in the extravascular space relative to the capillaries. This quasi state occurs during the "backflux phase" of the CTP acquisition (70 s–150 s). With this in mind, the IRF using this approximation can be calculated as follows [24]:

$$H(t) = -\left\{ \begin{matrix} 1 \\ Ee \end{matrix} \left[-\left(\frac{EF}{V_c}(t - T_c) \right) \right] \quad \begin{matrix} 0 \le t \le T_c \\ t > T_c \end{matrix} \right\} \tag{1}$$

where $H(t)$ is the IRF, E = the contrast extraction fraction, F = blood flow, V_c = the extravascular distribution of contrast, and time T_c = the minimum transit of the contrast bolus. According to the Rankin-Crone equation, PS (the permeability-surface area product) and E are described by the following relationship [24]:

$$E = 1 - e^{-\left(\frac{PS}{F}\right)} \tag{2}$$

Finally, by selecting an appropriate AIF (denoted by $C_a(t)$), the TAC (denoted by $Q(t)$) can be determined according to [24]:

$$Q(t) = F \cdot [C_a(t) * H(t - T_0)] \tag{3}$$

$*$ denotes the convolution operator, and $H(t - T_0)$ shifts $H(t)$ relative to the arrival of contrast the AIF. Parameters described in Fig. 1 are iteratively changed until an optimal fit to $Q(t)$ is reached.

For all patients, CTP functional maps were analysed in a standardized method by an experienced reader (C.D.D., >10 year experience) using multi-thresholding technique. Specifically, the CTP-perfusion weighted image (an average map generated from the raw CTP data to show anatomical contrast) was used to segment parenchyma from cerebrospinal fluid, ventricles, and skull using Hounsfield Unit (HU) thresholds (~35–100 HU range). Next, this anatomical mask was applied to the CBF functional map, which was used to separate ischemic tissue voxels - a threshold of CBF < 13 ml·min^{-1}·(100 g)$^{-1}$ as described previously as tissue that will infarct if reperfusion is not achieved (total tissue at risk). Within this ischemic mask, values of CBF, CBV and PS were obtained while excluding large vessels (CBV> 8 ml/100 g). The ischemic mask was then mirrored into the contralateral hemisphere to obtain the corresponding normal values for CBF, CBV and PS. For the PS parameter, ischemic PS values were divided contralateral PS values to obtain a relative PS for each patient.

Reperfusion was evaluated using the Thrombolysis in Cerebral Infarction score (TICI, with 2b/3 as successful reperfusion) and recanalization was evaluated using the arterial occlusive lesion score (AOL) in patients who underwent mechanical thrombectomy. The recanalization status in patients treated with intravenous thrombolysis (IV tPA) was assessed by a control CTA carried out within 24–32 h (complete, partial or none). Volume of infarction was measured semi-automatically in Quantomo® software. Midline shift was assessed at the level of the septum pellucidum (in mm) by a consensus of authors (O.V., P.C.). All readers were blinded to clinical information as well as follow-up data.

2.4. Statistical analysis

All analyses were performed with the use of Stata/SE 12.1 software (StataCorp LP). Baseline and outcome measures are presented as the mean and standard deviation (SD) for continuous variables, median and interquartile range (IQR) for categorical variables, and percentage for nominal variables. CTP parameters for patients with and without midline shift were compared with univariate Mann-Whitney Sum test. Receiver operator characteristic curves analysis with accuracy measures were obtained for each CTP parameter.

3. Results

Of 200 patients, seven of them (3.5%) had ≥5 mm midline shift. Two patients were excluded due to the presence of motion artefacts in CTP data. The 5 patients with midline shift were matched with 5 patients without midline shift based on admission ASPECTS, admission NIHSS and volume of ischemia on control imaging. Mean age in the ≥5 mm midline shift group was 61 years (standard deviation/SD ± 14), in the control group 78 years (SD ± 11). There was no significant difference in cardiovascular risk factors (hypertension, admission blood pressure, diabetes mellitus, dyslipidemia, atrial fibrillation, and coronary artery disease) between the two groups, Table 1. Six patients were treated with IV tPA (no recanalization on control CTA). Four patients underwent stent-retriever thrombectomy (MT) with reperfusion TICI 2b/3 and AOL III in all of these patients (time from symptom onset-to-recanalization ranged from 310 to 403 min). Midline shift of ≥5 mm has developed in three patients with MT and in two patients treated with IV tPA. There was no significant difference between the two groups in the mean values of CBF, CBV, and PS in the ischemic and contralateral mirror area, Table 2. A CBV threshold of 1.7 ml/100 g had the highest AUC = 0.72, 95% CI = 0.54–0.90 for midline shift, sensitivity and specificity were 0.83 (95% CI = 0.73–0.93) and 0.67 (95% CI = 0.55–0.80).

Table 1
Characteristics of study population.

Characteristics	All	Midline shift < 5 mm	Midline shift ≥ 5 mm	p-Value[a]
	N = 10	n = 5	n = 5	
Sex, female, n (%)	4 (40%)	1	3	0.52
Age, year, mean (SD)	69 (15)	78 (11)	61 (14)	0.07
NIHSS baseline, median (IQR)	22 (19–29)	22	22	0.95
NIHSS 24 h, median (IQR)	23 (14–24)	21	23	0.93
History of hypertension, n (%)	6 (60%)	4	2	0.52
Admission systolic blood pressure, mmHg, mean (SD)	143 (26)	141 (35)	144 (17)	0.85
Admission diastolic blood pressure, mmHg, mean (SD)	77 (16)	68 (11)	86 (15)	0.07
Diabetes mellitus, n (%)	1 (10%)	0	1	1
Dyslipidemia, n (%)	5 (50%)	4	1	0.2
Atrial fibrillation, n (%)	3 (30%)	2	1	1
Coronary artery disease, n (%)	1 (10%)	0	1	1
Admission ASPECTS, median (IQR)		9 (8–10)	9 (8–10)	0.95
Poor leptomeningeal collaterals, n (%)	3 (30%)	2	1	1
TICI 2b/3, n (%)	4 (40%)	1	3	0.03
Volume of infarction (mL), median (IQR)	214 (145–292)	227	210	0.5

SD – standard deviation, ASPECTS – Alberta Stroke Program Early CT Score, NIHSS – National Institutes of Health Stroke Scale, TICI – Thrombolysis in Cerebral Infarction, IQR – interquartile range, ICA – internal carotid artery, MCA – middle cerebral artery.

[a] Mann-Whitney or two-tailed Fisher test.

Table 2
Comparison of CTP parameters in the group with and without a significant midline shift.

CTP parameters		Midline shift < 5 mm	Midline shift ≥ 5 mm	p-Value[a]
		n = 5	n = 5	
Ischemic territory, mean (SD)	CBF	8.07 (7.34)	8.69 (8.20)	0.69
	CBV	1.94 (1.48)	1.21 (1.03)	0.06
	PS	1.76 (1.48)	2.29 (2.20)	0.13
Contralateral corresponding area, mean (SD)	CBF	37.96 (36.17)	42.69 (40.08)	0.11
	CBV	2.36 (2.19)	2.78 (1.91)	0.25
	PS	1.05 (1.11)	0.92 (1.19)	0.67
Relative PS, mean (SD)		1.87 (1.42)	3.52 (2.18)	0.20

CBF – cerebral blood flow, CBV – cerebral blood volume, PS – permeability surface area.
[a] Student *t*-test.

4. Discussion

In the small case-controlled data set, we showed that permeability analysis with an adequate scan length has a potential to differentiate between patients with and without midline shift in acute anterior circulation ischemic stroke.

Recent retrospective malignant brain edema prediction studies based on CTP analysis were devoted to analyse the BBB permeability in relation to malignant brain edema (number of patients with malignant edema: 3 and 12, respectively). Unlike our permeability analysis, these studies utilized the Patlak's model, or its modification, by commercially available software (Brain Perfusion Philips, Syngo Neuro PCT Siemens). These studies also differed in their technical approach to perfusion data acquisition (e.g. Bektas et al. used first-pass data, which poses a higher risk of data distortion in permeability analyses). This, among other things, affects quantitative comparisons with our data. Prospective CTP studies devoted to brain edema prediction were focused primarily on evaluating the admission CBF values of the ischemic territory [14,15]. One of them was focused on analysis of CBF maps acquired from PMZ-PET. However, this method is purely experimental and is not included in standard neuroimaging protocols in acute ischemic stroke due to logistical complexities.

A prospective study by Horsch et al. has brought new evidence that the CBV parameter and increased permeability of BBB are factors associated with space-occupying edema in anterior circulation stroke [25]. This is in accordance with our pilot results (CBV parameter had the highest accuracy for midline shift prediction, and there was also a trend for the mean PS values). Thus, the larger CBV ischemic deficit with increased permeability within the region might be considered as potential markers of malignant brain edema, and we consider these CTP parameters as target biomarkers for future studies. Using the same extended CTP acquisition, increased permeability of CT contrast at patient admission has been associated with hemorrhagic transformation (HT) [24]. However, red blood cell extravasation into the surrounding parenchyma requires large pore sizes within the endothelial cell wall, much larger than what would be required for ME. Therefore, we can speculate that at the snapshot of CTP imaging, the amount of CT contrast which extravasates in patients with ME is likely not discernable. Moreover, the pathophysiological process of malignant edema may not start until later in the ischemic cascade, and may even require reperfusion to the ischemic territory before the process even begins (reperfusion injury). Thus, the permeability analysis may be more useful for patients arriving late (>6 h from symptom onset).

We are aware the lower number of patients who we were able to enroll into the analyses (on the other hand, if we consider the malignant brain edema occurrence 3–10%, our incidence rate 3.5% is within the range). We are aware of the selection bias, which might have been caused by the matching procedure leading to age difference between the groups.

In contrast with majority of previously published studies, a well-defined prospective cohort has been studied and analysed. To have the opportunity to make some comparisons with previous studies aimed at predicting of malignant brain edema in patients with acute ischemic stroke, our pilot analysis also evaluated perfusion parameters for the entire region of detected acute ischemia, which might led to negative results of our pilot study. Nevertheless, to assess the predictive value of CT perfusion in the development of malignant brain edema we deem necessary to evaluate standardized data in larger and multicentre cohorts and analyse permeability in specific regions of interests within the ischemic territory.

Ethical standards and patient consent

We declare that all human studies have been approved by the [Calgary Stroke Program, Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Canada] and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

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Annex 2

OSPEL J. M., O. VOLNY, W. QIU, M. NAJM, N. KASHANI, M. GOYAL a B. K. MENON. Displaying Multiphase CT Angiography Using a Time-Variant Color Map: Practical Considerations and Potential Applications in Patients with Acute Stroke. American Journal of Neuroradiology [online]. 2020, 41(2), 200–205. ISSN 0195-6108.

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Displaying Multiphase CT Angiography Using a Time-Variant Color Map: Practical Considerations and Potential Applications in Patients with Acute Stroke

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ABSTRACT

SUMMARY: Various imaging protocols exist for the identification of vessel occlusion and assessment of collateral flow in acute stroke. CT perfusion is particularly popular because the color maps are a striking visual indicator of pathology. Multiphase CTA has similar diagnostic and prognostic ability but requires more expertise to interpret. This article presents a new multiphase CTA display format that incorporates vascular information from all phases of the multiphase CTA series in a single time-variant color map, thereby facilitating multiphase CTA interpretation, particularly for less experienced readers. Exemplary cases of multiphase CTA from this new display format are compared with conventional multiphase CTA, CT perfusion, and follow-up imaging to demonstrate how time-variant multiphase CTA color maps facilitate assessment of collateral flow, detection of distal and multiple intracranial occlusions, differentiation of pseudo-occlusion from real occlusion, and assessment of flow relevance of stenoses, ante- and retrograde flow patterns, and clot permeability.

ABBREVIATIONS: ACA = anterior cerebral artery; mCTA = multiphase CT angiography; PCA = posterior cerebral artery

Since the publication of multiple recent trials attesting to the benefit of thrombolysis and thrombectomy even in patients presenting late after stroke onset, fast and reliable detection of cerebrovascular pathology is ever more important. Several ongoing trials are using imaging to further expand treatment indications in patients with acute stroke. Imaging protocols designed for patients with acute stroke, therefore, need to be reliable in detecting and measuring a whole host of cerebrovascular pathology, including arterial flow dynamics across time, pial collateral status, distal arterial occlusions, and thrombus characteristics such as extent and permeability, carotid pseudo-occlusions, and venous thrombus, to name a few. Because acute stroke is a time-sensitive state in which any delay in decision-making affects patient outcome, such imaging protocols need to be easy to interpret for the average stroke physician in a small hospital. These imaging protocols also need to be easy to acquire and process without being affected too much by patient motion, a common occurrence when imaging patients with stroke.

Multiphase CTA (mCTA) provides time-resolved images of the cerebral vasculature that satisfy many of the above requirements for use in patients with acute stroke. The current display format of mCTA consists of 3 gray-scale images of the cerebral vasculature displayed side by side; visualization requires the reader to link these images together and scroll through them simultaneously. Interpretation, therefore, requires some degree of expertise. The technique was, however, used as a selection criterion for endovascular treatment in patients with acute ischemic stroke with large-vessel occlusions presenting <12 hours from symptom onset in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial and is being used in the ongoing Safety and Efficacy of NA-1 in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1; NCT02930018) and the A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion (TEMPO 2; NCT02398656) trials. Good collaterals as determined on CTA have also been shown to

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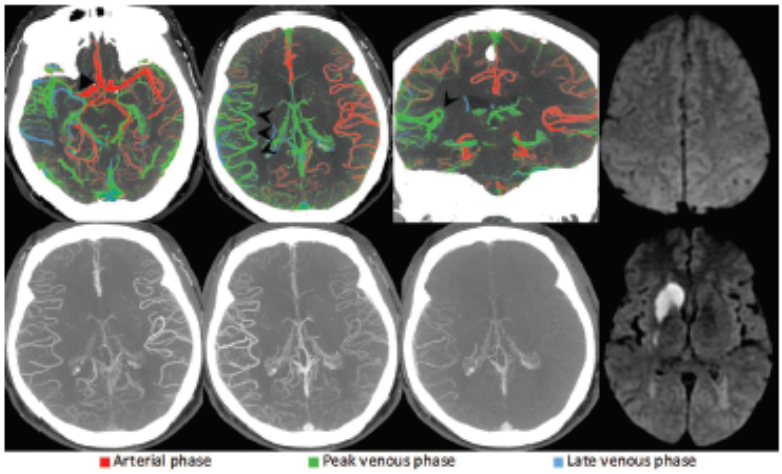

FIG 1. Right-sided M1 segment MCA occlusion (*arrow*). ColorViz summation maps (*upper row*) show predominantly green vessels in the affected territory (*arrowheads*), indicating a 1-phase delay. The vessel extent is identical to that of the unaffected hemisphere. The findings are consistent with good pial artery filling and collateral flow. Corresponding conventional mCTA images are displayed in the *lower row*. The patient received intravenous alteplase, and follow-up MR imaging 24 hours after symptom onset (*upper and lower right*) shows infarction of the caudate head and lentiform nucleus only, with sparing of the cortex.

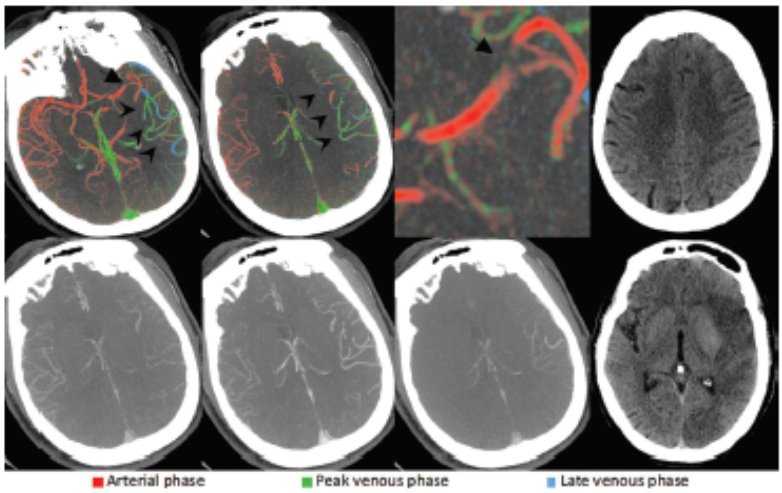

FIG 2. Left-sided M1 segment MCA occlusion (*arrow*). ColorViz summation maps (*upper row*) show predominantly green vessels (*arrowheads*) in the affected territory, indicating a 1-phase delay. However, the vessel extent is reduced compared with the unaffected hemisphere. Hence, the findings are consistent with intermediate pial artery filling and collateral flow. Corresponding conventional mCTA images are displayed in the *lower row*. The patient was treated with intravenous alteplase, and follow-up CT after 24 hours (*upper and lower right*) reveals an incomplete infarction pattern. While the insula, M1, and M2 regions are infarcted, the M3, M4, M5, and M6 regions are spared. Infarction is also present in the left PCA territory, indicating a fetal left PCA origin.

correlate with reduced infarct volume in patients presenting beyond 6 hours.[1] Most interesting, no association between collateral status and outcome was noted in this study.[1] CTP, another imaging technique with time-resolved images of parenchymal blood flow but with more complex acquisition and postprocessing, is considered easier to interpret because the display format is a single color-coded cerebral map of estimated blood flow and predicted tissue fate. This feature is in spite of obvious disadvantages of CTP, including longer image-acquisition times, susceptibility to patient motion, more radiation exposure, an additional contrast dose, a lack of whole-brain coverage, and complex and heterogeneous postprocessing algorithms. mCTA, on the other hand, requires no postprocessing, has a lower radiation dose, and can be acquired in <30 seconds (as opposed to CTP, which requires continuous scanning for 45–90 seconds), thereby minimizing motion artifacts.

In this primarily descriptive article, we present the case for a novel mCTA display format that encodes vascular information from all mCTA phases into a single color-coded map using a simple algorithm, thereby combining the indicator effect of color with the technical advantages of mCTA.

Patient Cohort

Imaging data were obtained are from the Precise and Rapid Assessment of Collaterals Using Multi-phase CTA in the Triage of Patients With Acute Ischemic Stroke for IA Therapy[2] a prospective observational multicenter study that seeks to analyze the incremental value of mCTA and CTP in acute ischemic stroke ($n = 596$). The local institutional ethics boards (University of Calgary, Foothills Medical center) approved the study. Patient baseline characteristics from this study are summarized in the On-line Table.

Image Acquisition and Interpretation

The details about the multiphase CTA acquisition technique, parameters, and image interpretation can be found in the On-line Appendix. Color-coded mCTA summation maps presented here were created on a workstation using the FastStroke research prototype (GE Healthcare, Milwaukee, Wisconsin), a CT image-analysis software package that is intended to display the full set of imaging information of

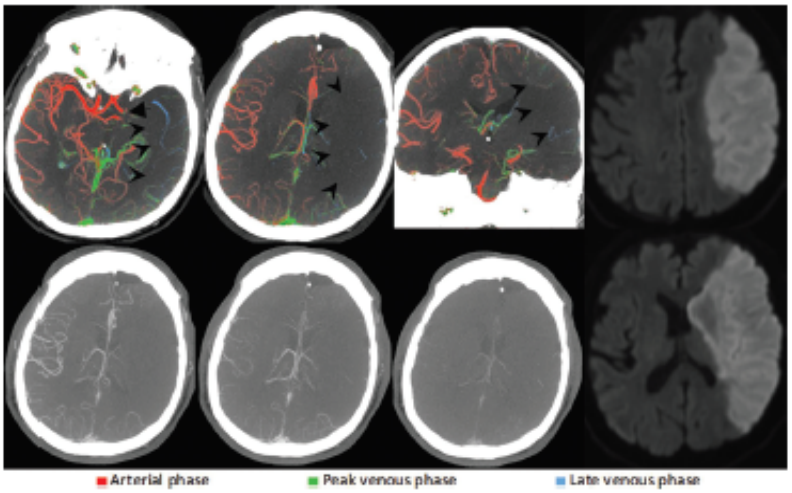

FIG 3. Left-sided ICA carotid L-occlusion (*arrow*). ColorViz summation maps (*upper row*) show a severely reduced vessel extent compared with the unaffected hemisphere (*arrowheads*). The few visible opacified vessels are predominantly blue, suggesting a 2-phase delay. This is consistent with poor pial artery filling and collateral flow. The patient was treated with antithrombotic therapy, and follow-up MR imaging after 24 hours (*upper and lower right*) shows complete infarction of the left MCA territory.

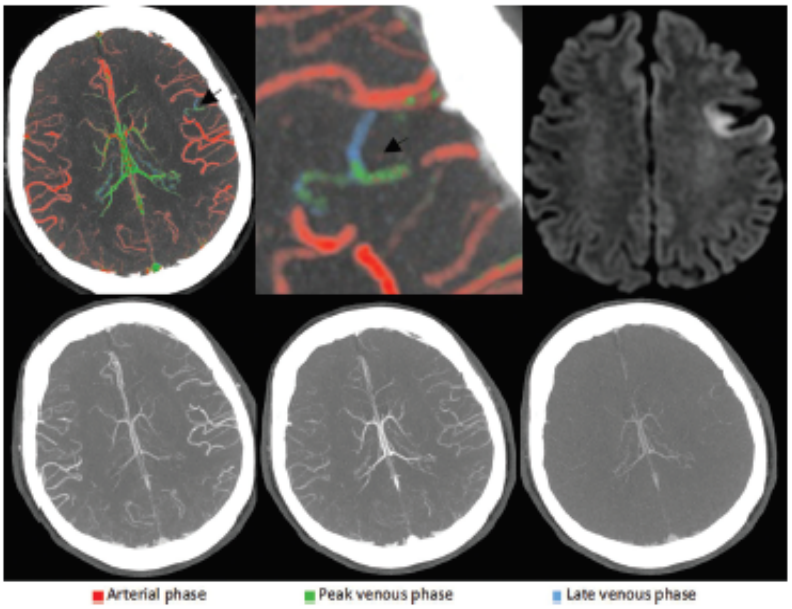

FIG 4. Left-sided M4 segment MCA occlusion. ColorViz summation images (*upper row*) show a focal area with blue and green vessels in the left frontal lobe (*black arrows*), ie, an area with delayed pial artery filling and washout, suggestive of a distal vessel occlusion. The thrombus itself cannot be visualized; the occlusion was detected on the basis of arterial flow information only. Corresponding conventional mCTA images in the *lower row* also show a slight delay in left frontal pial artery filling and washout; however, the occlusion is not as easily appreciable as in the color-coded summation maps. The patient received intravenous alteplase. Follow-up MR imaging after 24 hours (*upper right*) shows an acute left frontal lobe infarction, thereby confirming the suspected site of intracranial occlusion.

an advanced stroke CT imaging protocol (noncontrast CT, multiphase CTA, and CTP) in 1 single optimized, progressive workflow. The software fuses the vascular information from the different CTA phases (maximum of 9 phases) into a single color-coded view called ColorViz. It uses the original multiphase CTA thin slices to automatically display MIPs of the axial, coronal, sagittal, and oblique reformations. Colors are assigned on the basis of the timing and extent of contrast enhancement in the vessels and on a per-patient adaptive threshold technique; vessels maximally enhancing during the prevenous phase appear red; those that enhance in venous phase and venous phase are displayed in green and blue, respectively. The overall and phase-specific extent of pial en-hancement can then be quantified and compared with other territories in the contralateral hemisphere. Postprocessing is fully automated with the color-coded maps being available for review within 5–10 seconds. For evaluation of the vessel extent, the summation map can be switched to a single-color mode. Hence, the color display of the vasculature provides the full set of information about the dynamics and extent of pial artery filling from all mCTA phases in 1 single series. This feature expedites assessment of the intracranial vasculature compared with the conventional mCTA display format.

Evaluating Pial Arterial Filling/ Collateral Flow

mCTA is a reliable tool for assessment of pial artery filling in acute stroke imaging. Several studies (some single-center) have shown that it reduces interrater reliability and has excellent predictive validity with regard to clinical outcome.[2,3] It has, therefore, been used in past[4] and in ongoing clinical stroke trials such as ESCAPE NA1 and TEMPO 2. Pial artery filling is evaluated by assessing the extent of arterial filling and delay in that filling compared with the opposite side. A third metric is delayed washout of contrast within the pial arteries over the 3

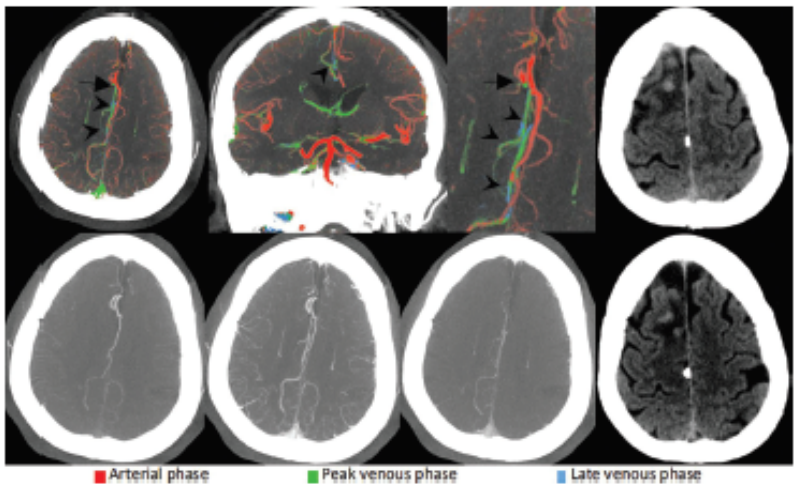

FIG 5. Right-sided A2 segment ACA occlusion (*arrows*). ColorViz summation images (*upper row*) show green and blue vessels distal to the occlusion (*arrowheads*), indicating impaired arterial filling within the right ACA territory. Corresponding conventional mCTA images are shown in the *lower row*. The patient received intravenous alteplase. Follow-up CT after 24 hours (*upper and lower right*) shows infarction in the right ACA territory.

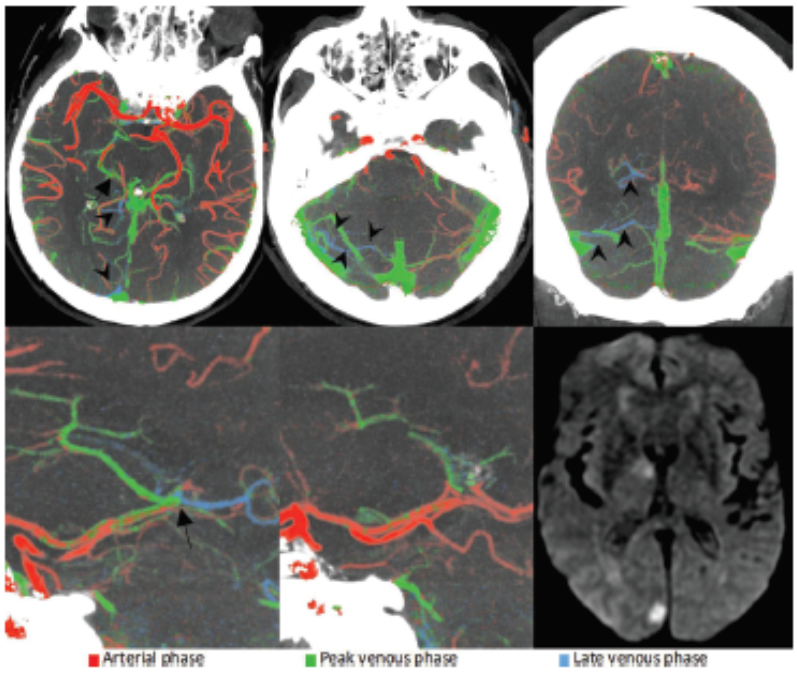

FIG 6. Right-sided fetal PCA occlusion (*arrows*). As opposed to the left PCA (*lower middle image*), the right distal PCA (*lower left image*) is blue in the color-coded summation images, suggestive of impaired filling of the distal vessel. The delayed arterial filling leads to a subsequent delay in venous filling in the posterior fossa on the affected side (*arrowheads*), a useful feature that is often encountered in posterior circulation occlusions and can help to identify the site of occlusion. Mechanical thrombectomy was performed. Follow-up MR imaging after 24 hours (*lower right*) reveals small right-sided occipital and thalamic infarct.

phases. Although pial artery filling and collateral flow are relatively easy to assess on conventional mCTA, the color-coded summation maps (ColorViz) further facilitate interpretation by combining all information into a single image and using a color-coded display format. Image-interpretation time is a few seconds for color-coded mCTA summation maps, as opposed to approximately 1 minute for conventional mCTA maps. An exemplary method for assessing collaterals on ColorViz based on assessing delay, extent, and washout within pial arteries is shown in Fig 1.

To assess pial artery filling using ColorViz, one visually determines the predominant vessel color (the color that is present in >40% of the vessels) in the affected vascular territory. Under normal circumstances, predominantly red vessels (such as the vessels on the contralateral side in Figs 1–3) indicate no delay, predominantly green vessels indicate a 1-phase delay (Fig 2), and predominantly blue vessels, a 2-phase delay (Fig 3). The absence of visible vessels in the affected territory indicates "no filling." Because diseases such as congestive heart failure can lead to a reduction in cardiac output and systemic flow delays, the predominant color in the unaffected hemisphere is also assessed and compared with the predominant color in the affected side. Of note, this correction cannot be applied to conditions that cause unilateral flow delays, such as flow-limiting proximal ICA stenosis, a limitation of mCTA. The extent of pial artery filling is scored in a single color mode by comparing vessel extent in the affected territory with that in the contralateral hemisphere. Differentiation of veins and arteries is based on their distinct flow characteristics (veins are usually displayed in green or blue because they enhance in the peak venous and late venous phases), filling direction, morphology, and anatomic location. The affected hemisphere may be considered to have good collateral flow if pial vessels distal to the occlusion are well-seen and are predominantly red or green (Fig 1).

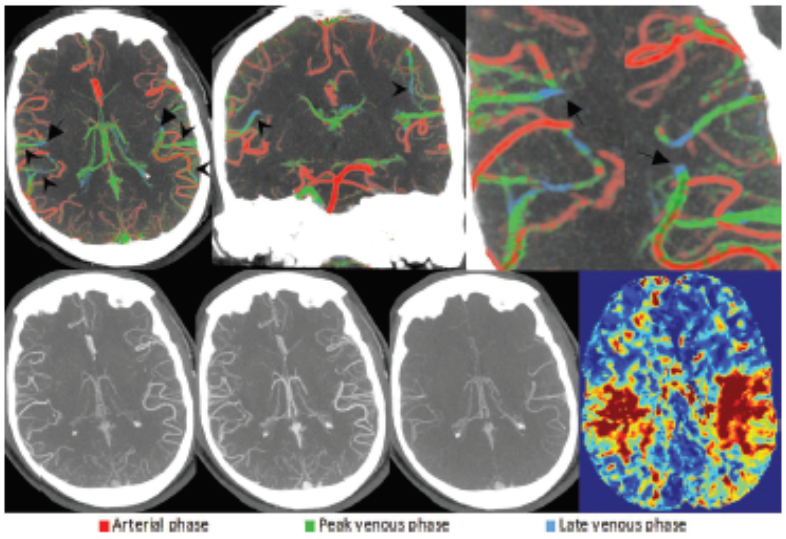

FIG 7. Bilateral M3 segment MCA occlusions (*arrows*) visualized through changes in the pial artery color compared with the surrounding pial arteries. Some cortical MCA branches of both hemispheres are depicted in green and blue (*arrowheads*), consistent with bilateral occlusions. Due to the symmetry of the occlusions, they are difficult to appreciate on conventional mCTA (*lower row*). CTP (*lower right*) shows prolonged time-to-maximum times in the affected territories, confirming the suspected occlusions.

Intermediate pial artery filling and collateral flow are present if either pial artery extent, pial artery filling, or both are moderately reduced in the affected territory (Fig 2). Most frequently, intermediate collateral flow manifests as green vessels (indicating a 1-phase delay) and reduced pial artery extent compared with the unaffected hemisphere.

Complete absence of pial artery filling or severely reduced extent and a 2-phase filling delay (ie, predominantly blue vessels) or complete absence of vessel opacification distal to the occlusion is considered poor pial artery filling (Fig 3).

Increasing Sensitivity in Vessel Occlusion Detection

While large-vessel occlusions are relatively easy to spot on single-phase CTA, distal occlusions are often missed.[5,6] Both CTP (by detecting ischemia in the color maps) and mCTA (through delayed collateral filling and washout) have been shown to improve distal-vessel-occlusion detection compared with single-phase CTA alone.[5-7] The additional color-indicator effect that is achieved using a color-coded display format and the ability to merge the vascular information in 1 rather than 3 series further facilitate detection of distal vessel occlusions on mCTA. The hallmark of distal occlusion in color-coded mCTA maps is areas of delayed flow manifesting as pial vessels in green and blue within 1 vascular territory (Fig 4).

Another advantage of color-coded mCTA summation maps is in detecting distal anterior cerebral artery (ACA) and posterior cerebral artery (PCA) occlusions (Figs 5 and 6). In theory, ACA and PCA occlusions can be easily detected on CTP by detecting perfusion abnormalities in the affected territories. However, the ACA and PCA territories are often not fully covered by the 4-, 8-, or 10-cm CTP slab that is frequently used with older generation scanners. Furthermore, mCTA does not succumb to skull base artifacts to the same extent as CTP and can therefore better visualize the posterior circulation. A particularly useful feature for posterior circulation occlusions is the venous filling delay in the posterior fossa, which results in a subsequent delay of venous filling, manifesting as an increased number of veins depicted in blue (Fig 6).

Detection of Multiple Intracranial Thrombi

Detecting intracranial thrombi other than the large-vessel occlusion that is easily identified is important because it may influence acute treatment strategies[8] and ultimately affect patient outcomes.[9] Color-coded mCTA is able to detect multiple intracranial occlusions in either the same (Fig 7) or different (On-line Fig 1) vascular territories.

CONCLUSIONS

Color-coded mCTA summation maps may facilitate easier assessment of acute stroke pathology, including better assessment of collateral status, distal occlusions, carotid pseudo-occlusions, intracranial stenosis, and thrombus permeability. ColorViz may be particularly useful for less experienced readers. Future work will, however, need detailed quantitative validation of each of the imaging constructs that ColorViz mCTA provides in patients with acute stroke.

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Annex 3

VANICEK J., P. CIMFLOVA, M. BULIK, J. JARKOVSKY, V. PRELECOVA, V. SZEDER a O. VOLNY (senior author). Single-Centre Experience with Patients Selection for Mechanical Thrombectomy Based on Automated Computed Tomography Perfusion Analysis-A Comparison with Computed Tomography Perfusion Thrombectomy Trials. Journal of Stroke & Cerebrovascular Diseases [online]. 2019, 28(4), 1085–1092. ISSN 1052-3057.

Single-Centre Experience with Patients Selection for Mechanical Thrombectomy Based on Automated Computed Tomography Perfusion Analysis—A Comparison with Computed TomographyCT Perfusion Thrombectomy Trials

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Background: In randomized clinical trials, mechanical thrombectomy (MT) was proved to be a highly effective treatment of acute ischemic stroke which improved clinical outcomes. Some of the trials used automated computed tomography perfusion (CTP) analysis for selection of participants. We present a single-center experience with CTP selection and comparison with CTP trials. *Methods:* Data of consecutive MT patients (from January 2016 to December 2017) were retrospectively reviewed. All patients with multiphase CT angiography confirmed the presence of anterior circulation large vessel occlusion/s in the intracranial internal carotid artery and/or middle cerebral artery (M1 or M2) and with admission brain CTP analyzed by RAPID software were included into the analysis. *Results:* Sixty-two patients fulfilled the inclusion criteria (mean age was 70.1 ± 13.6 years, females 48.5%). At baseline, National Institutes of Health Stroke Scale score was 16 (IQR = 13-20), Alberta Stroke Program Early CT Score (ASPECTS) was 8 (IQR = 7-9), CTP core volume was 20 mL (IQR = 2-36), and CTP penumbra volume was 145.5 mL (IQR = 107-184). Time from stroke onset to imaging was 1 hour 32 minutes, time from stroke onset to reperfusion was 3 hours 50 minutes, and median time from CT to reperfusion was 1 hour 56 minutes. Modified thrombolysis in cerebral infarction 2b/3 was achieved in 42 patients (67.7%). Twenty-three patients (37%) had modified Rankin scale 0-2 at 90 days. *Conclusions:* Our analysis of CTP-selected patients for MT supports clinical applicability of automated CTP analysis into everyday clinical practice.

Key Words: Mechanical thrombectomy—CT perfusion—RAPID—single-centre experience

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Level of Evidence: Level 4, Case series.

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Introduction

Recent randomized clinical trials (RCTs) demonstrated that mechanical thrombectomy (MT) with second-generation neurothrombectomy devices represents a highly effective and safe treatment for patients with acute ischemic stroke due to a large cerebral artery occlusion in the anterior cerebral circulation when performed within 6 hours after symptoms onset.[1-6]

Following trials with an extended time window for the treatment, DAWN (DWI or CT perfusion [CTP] Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke), showed the clinical benefit on 90 days functional outcome for thrombectomy patients who had last been known to be well between 6 and 24 hours prior to presenting stroke symptoms and who had the evidence of salvageable tissue on perfusion imaging.[7,8]

Since the neuroimaging protocol at our comprehensive stroke center from 2016 includes noncontrast computed tomography (CT), multiphase CT angiography (mCTA), and CTP evaluated automatically by RAPID software as used in all above mentioned perfusion trials, we decided to analyze real-world data and present our single-center experience and comparisons with above mentioned RCTs.

The main aim of our study was to compare short-term and long-term clinical outcomes in patients who were selected to undergo MT based on automated CTP analysis.

Methods

Patient Selection

Data of consecutive MT patients from January 2016 to December 2017 were retrospectively reviewed. All patients with mCTA confirmed presence of the anterior circulation large vessel occlusion in the intracranial internal carotid artery and/or middle cerebral artery (M1 or M2) and with admission imaging including mCTA and CTP were included into the analysis.

Ethics approval was obtained from the local Institutional Review Boards (the Boards waived the need for patient consent).

Imaging Protocol

Patients suspected of experiencing acute ischemic stroke and presenting no history of either renal failure or contrast allergy routinely undergo a noncontrast CT, mCTA from the aortic arch to vertex (Calgary Stroke Program protocol), and CTP.

Noncontrast CT was acquired on a multidetector scanner (120 kV, 328 mAs [419 mAs/slice], Brilliance iCT 256; Philips Healthcare, Cleveland, OH) with a section thickness of .9 mm and an image reconstruction of 3 mm.

For the CTP protocol, 40 mL of contrast agent (Iomeron 300; Mallinckrodt Pharmaceuticals; Dublin, Ireland) was power injected at 5 mL/s followed by a saline chase of 50 mL at 5 mL/s. Sections of 8 cm thickness were acquired at 10 mm slice thickness. Scanning began after a delay of 5 seconds from contrast injection in every 1.8 seconds for 75 seconds.

Image Processing

Commercially available automatic software (RAPID, iSchemaView) was used to generate perfusion maps and calculate volumes of ischemic core (regional Cerebral Blood Flow (CBF) <30%), critically hypoperfused tissue—ischemic penumbra (time to the maximum of the residue function [T_{max}] > 6 seconds) and mismatch volume.

Image Analysis

Patient study images (admission CT, mCTA, digital subtraction angiography studies, and 24-hour control CT) were assessed independently of each other by consensus of 2 experienced readers (P.C. and O.V.) during different sessions. Early ischemic changes were assessed on CT using the ASPECT scoring system. The collateral status was scored on the mCTA as good, moderate, or poor as previously described. Good collaterals were defined as pial vessels with no delay or a delay of 1 phase on mCTA in filling in when compared with the asymptomatic hemisphere, and normal extent within the ischemic territory. Moderate collaterals were defined as pial vessels with a delay of 2 phases in filling in and normal to decreased extent, or as pial vessels with a 1-phase delay and a significantly reduced number of vessels, or the presence of regions with no vessels within the ischemic territory. Poor collaterals were defined as just a few or no vessels visible in any phase within the ischemic territory.[9]

Final infarction was assessed using the ASPECTS on a 24-hour control CT and the presence or absence of haemorrhagic transformation was noted (ECASS II classification). Angiographic studies from the endovascular procedure were assessed for reperfusion using the modified thrombolysis in cerebral infarction (TICI) score. The modified TICI score is a 5-point scale that ranges from 0 (no reperfusion) to 3 (complete reperfusion of the previously ischemic territory) including grade 2c (almost complete reperfusion).[10]

Clinical Assessment

Clinical assessments were performed at baseline and included the National Institutes of Health Stroke Scale (NIHSS) score and, at 90 days by the modified Rankin scale (mRS), both were determined by certified raters.

Outcomes

The primary efficacy outcome was the ordinal score on the mRS, range: 0 (no symptoms) to 6 (death) at day 90.

The score was assessed in person, or by telephone if an in-person visit was not feasible. The secondary efficacy outcome was functional independence (defined as a score on the mRS of 0-2) at day 90. The primary safety endpoints were death within 90 days and the occurrence of symptomatic intracranial hemorrhage, defined as parenchymal hematoma type 2 on a 24-hour control CT.

The technical efficacy of the endovascular procedure was defined as a modified TICI score of 2b (50%-90% reperfusion) to 3 (complete reperfusion).

The procedure-related outcomes were characterized by the time from symptom onset to admission imaging (CT), the time from symptom onset to reperfusion, and the time from CT to reperfusion.

Statistical Analysis

Standard descriptive statistics was applied in the analysis; absolute, and relative frequencies for categorical variables and mean supplemented with standard deviation or median supplemented by interquartile range (IQR) for continuous variables. The relation of clinical endpoint and its potential predictors was analyzed using logistic regression and described by odds ratios, their confidence intervals, and statistical significance; $P = .05$ was taken as a level of statistical significance in all analyses. Statistical analysis was computed using the SPSS 25.0.0.1 software (IBM Corporation, 2017).

Medians of core/penumbra in our cohort and in the RCTs were compared. Statistical significance of difference between our cohort and the RCTs was estimated by using a 2 sample t test with following assumptions: (1) normal distribution of log transformed data and (2) standard deviation estimated from the IQR.

Results

From January 2016 to December 2017, a total number of 62 patients fulfilled the inclusion criteria (mean age was 70.1 ± 13.6 years, females 48.5%). Patients' characteristics are shown in Table 1. At baseline, the median NIHSS score was 16 (IQR = 13-20). The baseline median ASPECTS was 8 (IQR = 7-9). The median infarct volume was 20 mL (IQR = 2-36), median penumbra volume was 145.5 mL (IQR = 107-184). Comparison of our cohort with the CTP-thrombectomy trials is summarized in Table 2.

The median time from the stroke onset to imaging was 1 hour 32 minutes, median time from the stroke onset to reperfusion was 3 hours 50 minutes, and the median time from the CT to reperfusion was 1 hour 56 minutes (Table 3). The modified TICI 2b/3 was achieved in 42 patients (67.7 %). Twenty-three patients (37%) had mRS 0-2 at 90 days.

Table 4 summarizes results of univariate logistic regression.

Univariate models were constructed for each potential predictor and their effects were evaluated separately. In all models, the outcome measure was a 90-day mRS score of 0-2.

Discussion

In our analysis we evaluated real-world thrombectomy data from a high volume centre in the Czech Republic and compared the data with RCTs which used an automated CTP analysis (RAPID software) for patient selection.

From a demographic standpoint, our and above mentioned CTP-trials' cohorts were balanced in age, sex, admission NIHSS score, and comorbidities. From an imaging standpoint, our and CTP-trials' cohorts were balanced in admission ASPECTS and clot localization in the anterior cerebral circulation. Patients in our cohort had larger admission ischemic cores (median 20 mL) and penumbra (145 mL) in comparison to the CTP trials, which selected their participants according to perfusion mismatch (SWIFT PRIME, EXTEND IA, DEFUSE 3) or clinical/imaging mismatch (DAWN). The difference in the size of core was statistically significant in comparison to DAWN ($P = .001$) and DEFUSE study ($P = .019$). However, this estimated results needed to be taken with some cautious as the data was tested assuming the normal distribution within the particular patient cohorts. It was discussed previously that strict patient selection criteria might have potentially increased the rate of patients who had a good clinical outcome but, on the other hand, reduced treatment effect.[11] Our analysis showed that a significant predictor for good clinical outcome was the successful reperfusion (TICI 2b/3). There was no association of either good or poor clinical outcome with the volume of the ischemic core on admission CTP in our cohort. A possible explanation might be that all patients met the recommended perfusion criteria for ischemic core (defined as <50 mL in the SWIFT-PRIME trial) or less than 70 mL in the EXTEND-IA trial, respectively). These findings indicate that volume of the core is just 1 parameter and that clinical outcome is dependent on other variables such as the localization of core (eg, ischemic injury/damage to the motor corticospinal tract), the volume of salvagable penumbra and its localization in hypoperfused territory as well as the level and time of successful reperfusion.

Previous trials have demonstrated that workflow speed is strongly associated with better functional outcomes, thus the reduction of procedural times must be targeted in clinical practice.[12-14] The majority of patients included into our analysis were treated within the 6-hour time window from the symptom onset, which reflects efficient acute stroke care management at the regional level.[15] On the other hand, there is still a place for improvement at our centre, especially in door-to-groin and groin-to-reperfusion times.[16]

In terms of clinical outcome, defined as mRS 0-2 after 3 months, this single-centre experience showed comparable rates of good outcome with the SWIFT-PRIME trial (mRS 0-1 18% versus 20%; mRS 0-2 37% versus 35%). The relative decrease in the number of patients with a good 3-month clinical outcome in comparison to other throm-

Table 1. *Participants demographics, baseline imaging characteristics, procedural measures, and outcomes*

Variable	Category/descriptive statistics	Study group (N = 62)
Age-y	Mean ± standard deviation	70.1 ± 13.6
Sex-no. (%)		
	Males	32 (51.6 %)
	Females	30 (48.4 %)
Baseline NIHSS score		
	Median	16.0
	Interquartile range	13.0-20.0
Baseline CT ASPECTS		
	Median	8.0
	Interquartile range	7.0-9.0
Clot localisation, no. (%)		
	M1	45 (72.6 %)
	M2	7 (11.3 %)
	Terminal internal carotid artery	10 (16.1 %)
Pial collaterals, no. (%)		
	Poor	7 (11.3 %)
	Medium	28 (45.2 %)
	Good	26 (41.9 %)
RAPID core (mL)		
	Median	20.0
	Interquartile range	2.0-36.0
RAPID penumbra, mL		
	Median	145.5
	Interquartile range	107.0-184.0
RAPID mismatch, mL		
	Median	118.5
	Interquartile range	84.0-153.0
IV Thrombolysis, no. (%)		43 (69.4 %)
Procedural measures, h:min		
	Median time from stroke onset to groin puncture* (IQR)	2:45 (2:15-4:38)
	Median time from CT onset to reperfusion† (IQR)	1:56 (1:36-2:38)
	Median time from stroke onset to reperfusion‡ (IQR)	3:50 (3:00-5:27)
Thrombolysis in cerebral infarction, no. (%)		
	0-2a	20 (32.3 %)
	2b-3	42 (67.7 %)
Follow-up ASPECTS		
	Median	6.5
	Interquartile range	4.0-8.0
Haemorrhagic transformation, no. (%)		
	HI1 + HI2 + PH1	15 (24.2 %)
	PH2	2 (3.2 %)
Modified Rankin scale 3 mo, no. (%)		
	0-1	11 (17.7 %)
	0-2	23 (37.1 %)
Comorbidities, no. (%)		
Hypertension		49 (79.0 %)
	Hyperlipidemia	30 (48.4 %)
	Diabetes mellitus	16 (25.8 %)
	Atrial fibrillation	23 (37.1 %)
	Smoking (previous or current)	9 (14.5 %)
	Ischemic heart diseases	23 (37.1 %)
	Previous stroke	7 (11.3 %)

Abbreviations: CT, computed tomography; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.
*counted on smaller N = 51, due to some patients missing data.
†counted on smaller N = 50, due to some patients missing data.
‡counted on smaller N = 44, due to some patients missing data.

Table 2. *Comparison of Brno thrombectomy data with randomized clinical trial using automated CTP analysis (RAPID)*

Variable	Category	Brno (N = 62)	SWIFT PRIME (N = 98)	EXTEND IA (N = 35)	DAWN (N = 107)	DEFUSE (N = 92)
Age, y	Mean ± SD	70.1 13.6	65.0 ± 12.5	68.6 ± 12.3	69.4 ± 14.1	70.0 (59.0-79.0)
Sex, no. (%)						
	Male	32 (51.6 %)	54/98 (55 %)	17 (49 %)	51 (52 %)	46 (50 %)
NIHSS score						
	Median	16.0	17.0	17.0	17.0	16.0
	IQR	13.0-20.0	13.0-19.0	13.0-20.0	13.0-21.0	10.0-20.0
CT ASPECTS						
	Median	8.0	9.0	NA	NA	8.0
	IQR	7.0-9.0	7.0-10.0			7.0-9.0
Clot localisation, no. (%)						
	M1	45 (72.6 %)	62/93 (67 %)	20 (57 %)	83 (78 %)	60 (65 %)
	M2	7 (11.3 %)	13/93 (14 %)	4 (11 %)	2 (2 %)	
	ICA	10 (16.1 %)	17/93 (18 %)	11 (31 %)	22 (21 %)	32 (35 %)
Collaterals, no. (%)						
	Poor	7 (11.3 %)	NA	NA	NA	NA
	Medium	28 (45.2 %)				
	Good	26 (41.9 %)				
RAPID core, mL						
	Median	20.0	Target perfusion mismatch 83/98 (85 %)*	12.0	7.6	9.4
	IQR	2.0-36.0		4.0-32.0	2.0-18.0	2.3-25.6
Core volume Brno versus other groups, *P* value†		-	-	.218	.001	.019
RAPID penumbra, mL						
	Median	145.5		106.0		114.7
	IQR	107.0-184.0		76.0-137.0		79.3-146.3
Penumbra volume Brno versus other groups, *P* value†		-	-	<.001	-	.001
RAPID mismatch						
	Median	118.5				
	IQR	84.0-153.0				
IV Thrombolysis-no. (%)		43 (69.4 %)	31/98 (32 %)	100%	5 (5 %)	10 (11 %)
TICI 2b/3		42 (67.7 %)	73/83 (88 %)	25/29 (86 %)	90 (84 %)	69/91 (76 %)
		Follow-up ASPECTS	NA	NA	24h-infarct volume	24h-infarct volume
Control imaging	Median	6.5			8.0 cc	35.0 cc
Extent of infarction	IQR	4.0-8.0			.0-48.0	18.0-82.0
Hemorrhagic transformation-no. (%)		PH2	PH2	PH2	SICH	PH2
		2 (3.2 %)	1 (1 %)	0 (0 %)	6(6 %)	8 (9 %)

(*Continued*)

Table 2 (*Continued*)

Variable	Category	Brno (N = 62)	SWIFT PRIME (N = 98)	EXTEND IA (N = 35)	DAWN (N = 107)	DEFUSE (N = 92)
mRS 3 mo, no. (%)						
	0-1	11 (18 %)	20 (20 %)	18 (52 %)	31%	26%
	0-2	23 (37 %)	36 (35 %)	25 (72 %)	48%	54%

Abbreviations: CTP, computed tomography perfusion; ICA, internal carotid artery; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TICI, thrombolysis in cerebral infarction.

*The target mismatch profile was defined as the core infarct lesion measured 50 mL or less, the volume of tissue with a time to maximum delay of more than 10 s was 100 mL or less, and the mismatch volume was at least 15 mL and the mismatch ratio was more than 1.8.

†Statistical significance of difference between our cohort and the RCTs was estimated by using a 2 sample *t* test with following assumptions: (1) normal distribution of log transformed data and (2) standard deviation estimated from the IQR.

Table 3. *Comparison of procedural times*

	Brno (N = 62)	SWIFT PRIME (N = 98)	EXTEND IA (N = 35)	DAWN (N = 107)	DEFUSE (N = 92)
Time interval-h:min					
Symptom onset to groin puncture* (IQR)	2:45 (2:15-4:38)	3:44 (2:45-4:35)	3:30 (2:46-4:11)	NA	NA
CT to reperfusion* (IQR)	1:56 (1:36-2:38)	0:57 (0:40-1:20)	1:33 (1:11-2:18)	NA	0:59
Stroke onset to reperfusion* (IQR)	3:50 (3:00-5:27)	NA	4:08 (3:24-4:37)	NA	NA

Abbreviations: CT, computed tomography; IQR, interquartile range.

*The time interval expressed as the median.

Table 4. *Relation of clinical result mRS 0-2 (endpoint) with predictors*

Univariate logistic regression		N	endpoint	OR (95% CI)	*P* value
Age					
	<70	27	10 (16.1 %)	-	-
	70+	35	13 (21.0 %)	1.01 (.36-2.84)	.99
Sex					
	Female	30	6 (9.7 %)	-	-
	Male	32	17 (27.4 %)	4.53 (1.46-14.07)	**.01***
NIHSS score					
	Median and less	36	15 (24.2 %)	-	-
	More than median	26	8 (12.9 %)	.62 (.22-1.80)	.38
CT ASPECTS					
	Median and less	38	14 (22.6 %)	-	-
	More than median	24	9 (14.5 %)	1.03 (.36-2.96)	.96
Clot localisation					
	M1	45	17 (27.4 %)	-	-
	M2	7	4 (6.5 %)	2.43 (.46-12.81)	.30
	ICA +tICA	10	2 (3.2 %)	5.33 (.62-45.99)	.13
Collaterals					
	Good	26	11 (18.0 %)	-	
	Medium	28	10 (16.4 %)	.23 (.02-2.17)	.20
	Poor	7	1 (1.6 %)	.76 (.25-2.27)	.62
RAPID core					
	20 mL and more	32	11 (17.7 %)	-	-
	10-20 mL	9	3 (4.8 %)	1.43 (.46-4.44)	.53
	0-10 mL	21	9 (14.5 %)	.96 (.20-4.57)	.95
IV Thrombolysis					
	No	18	7 (11.5 %)	-	-
	Yes	43	16 (26.2 %)	.93 (.30-2.89)	.90
TICI					
	Other	21	3 (4.8 %)	-	-
	2b-3	42	20 (32.3 %)	5.71 (1.46-22.42)	**.01***
HTN					
	No	13	5 (8.1 %)	-	-
	Yes	49	18 (29.0 %)	.93 (.26-3.27)	.91
HLP					
	No	32	9 (14.5 %)	-	-
	Yes	30	14 (22.6 %)	2.24 (.78-6.41)	.13
DM					
	No	19	19 (30.6 %)	-	-
	Yes	4	4 (6.5 %)	.47 (.13-1.70)	.25
AFib					
	No	39	17 (27.4 %)	-	-
	Yes	23	6 (9.7 %)	.46 (.15-1.41)	.17
Smoking					
	No	53	18 (29.0 %)	-	-
	Yes	9	5 (8.1 %)	2.43 (.58-10.18)	.22
IHD					
	No	39	15 (24.2 %)	-	-
	Yes	23	8 (12.9 %)	.85 (.29-2.50)	.77
Previous stroke					
	No	55	22 (35.5 %)	-	-
	Yes	7	1 (1.6 %)	.25 (.03-2.22)	.21
Time from stroke onset to CT					
	Median and less	26	10 (18.9 %)	-	-
	More than median	27	11 (20.8 %)	1.10 (.37-3.31)	.87
Time from stroke onset to reperfusion					
	6 h and less	37	18 (40.9 %)	-	-

(*Continued*)

Table 4 (*Continued*)

Univariate logistic regression		N	endpoint	OR (95% CI)	*P* value
	More than 6 h	7	3 (6.8 %)	.96 (.30-3.22)	.97
Time from CT to groin puncture					
	Median and less	29	13 (22.0 %)	-	-
	More than median	30	10 (16.9 %)	.62 (.21-1.77)	.37
Time from CT to reperfusion					
	Median and less	25	13 (26.0 %)	-	-
	More than median	25	9 (18.0 %)	.52 (.17-1.61)	.26

Abbreviations: AFib, Atrial Fibrillation; CI, confidence intervals; CT, computed tomography; DM, Diabetes Mellitus; HLP, Hyperlipoproteinemia; HTN, Hypertension; IHD, Ischemic Heart Disease; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TICI, thrombolysis in cerebral infarction.

*TICI 2b-3 and also the male sex were statistically significant.

bectomy trials might be explained by lower rates of successful reperfusion and the nonrandomized design of our study (TICI 2b/3 67.7% versus 76%-88%). Additionally, the fact that patients in our cohort had larger cores may reflect in the lower rates of good clinical outcome. In a recent study by Rebello et al,[17] it was demonstrated that patients with large cores (more than 50 mL) and large mismatch profiles may still benefit from endovascular treatment, and reach a favourable shift in the distribution of 90-day mRS score. However, the rate of good clinical outcome (mRS 0-2) was lower (25%) in comparison to the trials with relatively small cores.

Our study has several limitations. We are aware that our comparisons with the RCTs are merely qualitative, since our data are based on retrospective and single-center analysis with a relatively limited number of patients. The aim of this study was to evaluate the effect of using the multimodal imaging protocol for the selection of patients indicated to MT and the correlation with the final clinical outcome, so only patients with admission CTP imaging were included. As clinical evaluation of disability and outcome (NIHSS and mRS) was not completely blind, there may be a source of bias.

In conclusion, our analysis of CTP-selected patients for MT supports clinical applicability of automated CTP analysis into everyday clinical practice. Multimodal imaging protocols have a potential to better distinguish patients with a malignant CTP profile and thus prevent futile reperfusion as well as avoid excluding patients who may still benefit from the endovascular treatment regardless the time of onset or in patients with unknown time of onset.

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Annex 4

VOLNY O., M. BAR, A. KRAJINA, P. CIMFLOVA, L. KASICKOVA, R. HERZIG, D. SANAK, O. SKODA, A. TOMEK, D. SKOLOUDIK, D. VACLAVIK, J. NEUMANN, M. KOCHER, M. ROCEK, R. PADR, F. CIHLAR a R. MIKULIK. A Comprehensive Nationwide Evaluation of Stroke Centres in the Czech Republic Performing Mechanical Thrombectomy in Acute Stroke in 2016. Ceska a Slovenska Neurologie a Neurochirurgie [online]. 2017, 80(4), 445–450. ISSN 1210-7859.

Systematická evaluace center provádějících mechanické trombektomie u akutního mozkového infarktu v České republice za rok 2016

A Comprehensive Nationwide Evaluation of Stroke Centres in the Czech Republic Performing Mechanical Thrombectomy in Acute Stroke in 2016

Souhrn

Úvod: Mechanická trombektomie (MT) je standardní léčba pacientů s akutním mozkovým infarktem. Proto jsme se rozhodli systematicky zhodnotit činnost center provádějících MT v České republice. *Metody:* Do všech center vysoce specializované péče zajišťujících MT u pacientů s akutním iktem byl rozeslán online dotazník vycházející z mezinárodních doporučení, který monitoroval výkony provedené za rok 2016 (64 otázek zaměřených na zobrazovací metody, logistiku péče a trénink lékařů). *Výsledky:* Návratnost dotazníku byla 100%. Ve 14 centrech jsou vypracovány tzv. lokální standardy. Všechna centra disponují specializovanými iktovými jednotkami. CT v režimu 24/7 je k dispozici ve všech a 24/7 MR v 11 centrech. Vstupní zobrazení v okně do 6 hod: CT/CTA v 11, CT/CTA/CTP v 6, MR/MRA ve 2 centrech; po 6 hod od vzniku příznaků: CT/CTA v 7, CT/CTA/CTP ve 14 a MR/MRA v 5 centrech. Časné ischemické změny jsou hodnoceny ve všech centrech a kolaterální cirkulace v 8 centrech. Intervenční specialista v režimu 24/7 je k dispozici ve všech centrech. Čas příjezd–punkce třísla < 60 min je sledován ve 14 a příjezd–dosažení reperfuze < 90 min v 10 centrech. Ve všech centrech je preferována analgosedace před celkovou anestezií. Do registru (SITS-TBY) vkládá data 14/15 center. V roce 2016 bylo provedeno 1 053 MT (rozptyl: 17–136/centrum). V roce 2016 bylo v České republice trénováno 49 lékařů a celkem 64 lékařů provádělo MT. *Závěr:* Výsledek sebehodnotícího dotazníku ukazuje, že Česká republika obecně disponuje dobrou dostupností a odbornou úrovní v poskytování MT u akutního mozkového infarktu. Nicméně mezi centry existuje vysoká variabilita. Dalším krokem je kontinuální evaluace kvality prováděných MT, a to na úrovni údajů od jednotlivých pacientů.

Abstract

Introduction: Mechanical thrombectomy (MT) has been established as a standard of care in acute ischaemic stroke. We systematically evaluated all stroke centres conducting MT in the Czech Republic. *Methods:* An online questionnaire based on the International Multi-Society Consensus Document was distributed to all such centres to monitor all the procedures in 2016. It includes 64 questions on imaging, logistic and training standards related to MT. *Results:* Complete data were obtained from all 15 comprehensive stroke centres. Local operating procedures are used in 14 centres. Specialised stroke units are available in all centres, 24/7 CT is available in all centres and 24/7 MRI in 11 centres. Admission imaging in a time window < 6 hours includes: CT/CTA in 11, CT/CTA/CTP in 6, MRI/MRA in 2 centres; after 6 hours from the symptoms: CT/CTA is performed in 7, CT/CTA/CTP in 14, MRI/MRA in 5 centres. Early ischaemic changes are evaluated before neuro-intervention in all centres and collaterals are scored in 8 centres. Interventionalists are available 24/7 in all centres. Door-to-groin time < 60 min is monitored in 14 and door-to-reperfusion < 90 min in 10 centres. Analgosedation is preferred over general anaesthesia in all centres. Fourteen centres enter data into a registry (SITS-TBY). Approximately 1,053 MTs (range: 17–136/centre) were performed in 2016. There are 46 neuro-interventional trainees and 64 interventionalists providing MT in 2016. *Conclusion:* The Czech Republic has a high availability of expertise to perform MT in acute ischaemic stroke. Nevertheless, there is a high variability among the centers. Thus, the next step should be regular quality monitoring and evaluation of patients' data.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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mechanická trombektomie – mozkový infarkt – dotazník – celonárodní evaluace

Key words

mechanical thrombectomy – acute stroke – questionnaire – nationwide evaluation

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Úvod

Randomizované multicentrické studie (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT a EXTEND IA) a metaanalýza výše uvedených studií (HERMES) jednoznačně prokázaly, že mechanická trombektomie (MT) představuje vysoce účinnou a bezpečnou léčbu akutního mozkového infarktu při akutním uzávěru velké mozkové tepny v přední mozkové cirkulaci (intrakraniální segment *arteria carotis interna* (ACI) a/nebo proximální segment *arteria cerebri media* (ACM); Třída 1, úroveň evidence A) [1–6]. MT představuje jeden z nejúčinnějších terapeutických postupů v medicíně (abychom jednoho pacienta kompletně vyléčili, stačí léčit 2–3 pacienty; dle metaanalýzy HERMES ze 100 pacientů léčených MT 38 dosáhlo lepšího výsledného klinického stavu ve srovnání se intravenózní trombolýzou (IVT) a dalších 20 dosáhlo funkční nezávislosti hodnocené pomocí modifikované Rankinovy škály (mRS): 0–2) [6]. Finanční analýzy nákladů a přínosů ukazují, že účinná terapie MT vede rovněž k ekonomické úspoře u efektivně léčených pacientů [7,8].

Proto je nezbytné, aby zřizovatelé zdravotnické péče, odborné lékařské společnosti, nemocnice a lékaři v České republice:

1. zajistili odpovídající dostupnost této metody všem potenciálním kandidátům MT;
2. byly provedeny nezbytné organizační změny, které umožní tuto účinnou léčbu efektivně aplikovat;
3. MT byly prováděny s cílem dosažení takových časových parametrů a parametrů kvality, aby efektivita byla na srovnatelné úrovni s výše uvedenými klinickými studiemi.

Proto je nutné definovat organizační a logistické kroky na regionální a národní úrovni, definovat národní a mezinárodní standardy vzdělávání a formálního tréninku lékařů/specialistů a důsledně monitorovat kvalitu prováděných výkonů. Detailní mezinárodní doporučení jsou k dispozici v recentně publikovaném konsenzu mezinárodních odborných společností: Training Guidelines for Endovascular Ischemic Stroke [9]. Kontrola kvality neurointervenčních výkonů je definována mezinárodními doporučenými postupy (guidelines) European Stroke Organization (ESO) a American Heart Association/American Stroke Association (AHA/ASA) a národními doporučenými postupy v České republice [10,11].

Cílem našeho dotazníkového šetření podpořeného odbornými společnostmi (Cerebrovaskulární sekce České neurologické společnosti (CVS ČNS) a České společnosti intervenční radiologie (ČSIR)) je poskytnout základní informace o způsobu MT u akutního mozkového infarktu v České republice (pozn. autorů – poslední zhodnocení komisemi jmenovanými ministerstvem zdravotnictví proběhlo v roce 2010).

Materiál a metodika

Do všech 15 center provádějících MT v České republice byl v prosinci roku 2016 rozeslán online dotazník *(tzv. Centra vysoce specializované cerebrovaskulární péče – 13 center a Centra vysoce specializované péče o pacienty s iktem – 2 centra)*, jehož cílem bylo monitorovat výkony provedené v kalendářním roce 2016 [12,13]. Soubor otázek byl vytvořen na základě spolupráce a oborové diskuze CVS ČNS a ČSIR.

Centra byla instruována, aby byl dotazník vyplněn formou konsenzu lékařů zapojených do diagnostiky a léčby akutního mozkového infarktu (blíže specifikováno nebylo). V případě nekompletních údajů ve vyplněném dotazníku byli vedoucí zástupci jednotlivých center kontaktováni emailem (rozeslán CVS ČNS) s cílenými dotazem na chybějící nebo neúplná data.

Dotazník obsahoval celkem 64 otázek: otázky s možností výběru 1 odpovědi, s možností výběru více odpovědí, některé otázky umožňovaly navíc i textovou odpověď. Otázky byly zaměřeny na logistiku péče v rámci centra, indikační kritéria k MT, protokoly zobrazovacích metod používané v rámci indikace pacienta k neurointervenčnímu výkonu v různých časových intervalech od vzniku příznaků iktu, na monitoraci časových parametrů výkonu. Poslední sekce dotazníku byla věnována tréninku lékařů provádějících MT.

Statistická analýza

Byla provedena deskriptivní analýza jednotlivých parametrů pomocí statistického softwaru SPSS 24 (IBM, USA).

Výsledky

Kompletní dotazníková data byla získána ze všech 15 center (tab. 1). V roce 2016 bylo dle dostupných dat v České republice provedeno 1 053 MT u akutního mozkového infarktu (rozptyl 17–136 výkonů/centrum) (obr. 1).

Logistika péče

Ve 14 centrech jsou vypracovány lokální standardy, tzv. standard operating procedures (SOP). Specializovanými iktovými jednotkami disponují všechna centra. Výpočetní tomografie (CT) v režimu 24/7 je k dispozici ve všech centrech, v 11 centrech je v režimu 24/7 dostupná i magnetická rezonance (MR), a to včetně akutních radiologických popisů.

Vstupní zobrazení v časovém okně do 6 hod: v 11 centrech je prováděno CT/CT angiografie (CTA), v 6 centrech CT/CTA/CT perfuze (CTP) – u vybraných pacientů a ve 2 centrech MR/MR angiografie (MRA). Po 6 hod od vzniku příznaků je ve 14 centrech prováděno CT/CTA/CTP, v 7 centrech pouze CT/CTA

Tab. 1. Základní charakteristiky center provádějících MT v České republice v roce 2016.

Počet center provádějících MT v ČR v roce 2016, n	**15**
Existence lokálních standardů pro MT, n (%)	14 (93)
24/7 dostupnost CT a radiologa, n (%)	15 (100)
24/7 dostupnost MR a radiologa, n (%)	11 (73)
Standard zobrazení u suspekce na uzávěr velké mozkové tepny v časovém okně < 6 hod:	
- CT/CTA	11 (73)
- CT/CTA/CTP	6 (40)
- MR/MRA	1 (7)
Standard zobrazení u suspekce na uzávěr velké mozkové tepny v časovém okně > 6 hod anebo u nejasné doby vzniku:	
- CT/CTA	7 (47)
- CT/CTA/CTP	8 (53)
- MR/MRA	1 (7)
Hodnocení časných ischemických změn pomocí CT-ASPECTS nebo MR-ASPECTS před výkonem, n (%)	12 (80)
Hodnocení morfologie leptomeningeálních kolaterál před výkonem, n (%)	8 (53)
24/7 dostupnost stroke neurologa, n (%)	14 (93)
24/7 dostupnost intervenčního radiologa, n (%)	15 (100)
24/7 dostupnost angio-linky, n (%)	15 (100)
24/7 dostupnost cévního chirurga, n (%)	15 (100)
Sledování času příjezd–punkce třísla (door-to-groin) < 60 min, n (%)	14 (93)
Sledování času příjezd–reperfuze (door-to-reperfusion) < 90 min, n (%)	10 (67)
Hodnocení dosažené reperfúze radiologem (používaná skóre):	
- skóre TICI	12 (80)
- skóre mTICI s kategorií TICI 2c	3 (20)
Monitorace celkového počtu zavedení stent-retrieveru a počtu extrakcí, n (%)	11 (73)
Použití instrumentária k ošetření místa vpichu (tzv. artery closure device), n (%)	13 (87)
Monitorace embolizace do nového teritoria na finálním DSA nástřiku, n (%)	13 (87)
Monitorace peri- a postprocedurálních komplikací, n (%)	15 (100)
Preference analgosedace před celkovou anestezií, n (%)	13 (87)
Export DSA snímků do PACS (před výkonem, během výkonu, finální)	15 (100)
Vkládání dat o MT do registru SITS-TBY, n (%)	14 (93)
Trénink v neurointervencích:	
- celkový počet lékařů trénovaných v MT v České republice v roce 2016, n (rozptyl/centrum)	49 (1–5)
- probíhající trénink jiných specializací než radiologie * (kardiologie/angiologie)	3
- celkový počet intervenčních lékařů provádějících MT v České republice v roce 2016, n (rozptyl/centrum)	64 (2–6)

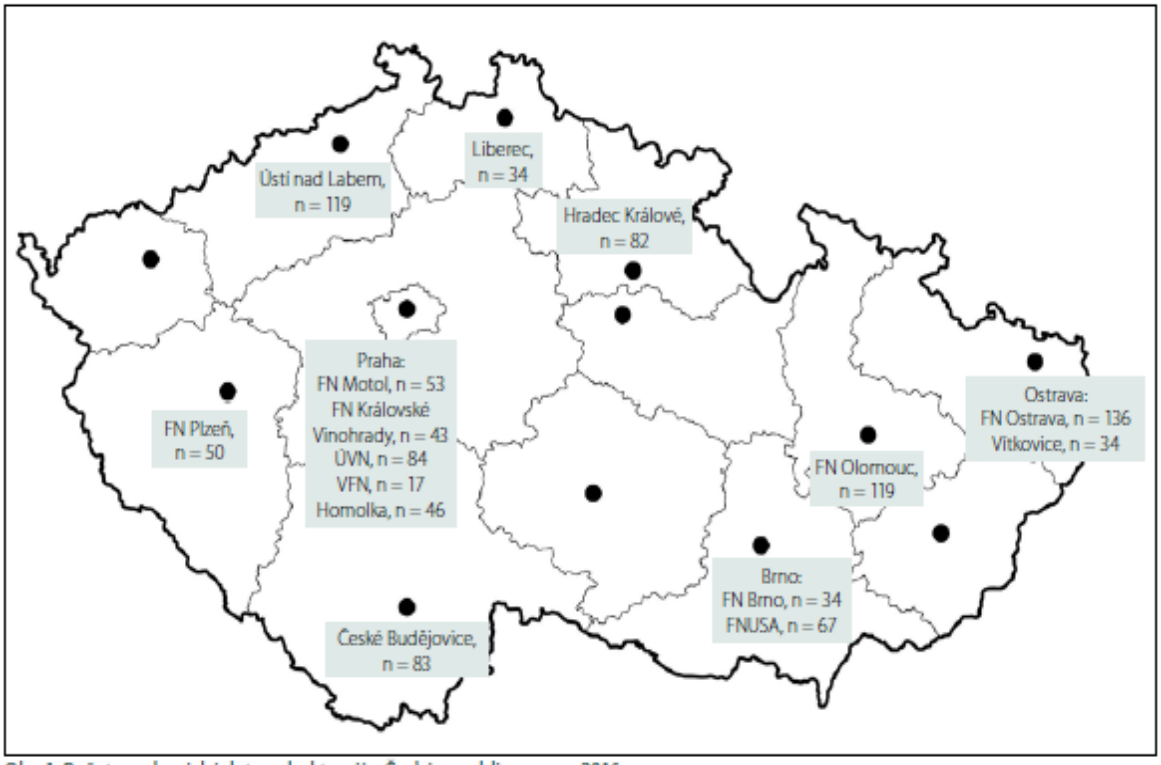
MT – mechanické trombektomie, CT – počítačová tomografie, MR – magnetická rezonance, CTA – CT angiografie, CTP – CT perfúze, MRA – MR angiografie, ASPECTS – Alberta Stroke Program Early CT Score, TICI – Thrombolysis in Cerebral Infarction, mTICI - modified Thrombolysis in Cerebral Infarction, DSA – digitální subtrakční angiografie.

a v 5 centrech MRI/MRA (výběr zobrazovacích metod závisí na indikujícím lékaři).

V rámci zobrazovacích indikačních kritérií všechna centra uvedla, že hodnotí rozsah časných ischemických změn (dominantně pomocí škály Alberta Stroke Program Early CT Score (ASPECTS), v 8 centrech je v rámci indikace pacienta k výkonu prováděno hodnocení kolaterální cirkulace. Ve všech centrech je dobrá dostupnost (v dotazníku definována jako dostupnost v režimu 24/7 vč. možnosti telefonických konzultací) neurologa specializujícího se na diagnostiku a léčbu akutních mozkových infarktů, intervenčního radiologa, angio-linky a cévního chirurga (tab. 1).

Monitorace kvality neurointervenčních výkonů

V rámci časových parametrů neurointervenčních výkonů jsou monitorovány a re-



Obr. 1. Počet mechanických trombektomií v České republice v roce 2016.

ÚVN – Ústřední vojenská nemocnice, VFN – Všeobecná fakultní nemocnice, FNUSA – Fakultní nemocnice u sv. Anny.

Fig. 1. Number of mechanical thrombectomy interventions in the Czech Republic in 2016.

ÚVN – Military University Hospital Prague, VFN – General University Hospital in Prague, FNUSA – St. Anne's University Hospital Brno.

portovány následující doporučené parametry: čas příjezd–punkce třísla (door-to-groin time) < 60 min ve 14 centrech a čas příjezd–dosažení reperfúze (door-to-reperfusion time) < 90 min v 10 centrech [14]. K datu publikování tohoto článku však nebyly k dispozici přesné časové údaje.

Z technických parametrů výkonu

Ve všech centrech je preferována analgosedace před celkovou anestezií. Jedenáct z 15 center uvedlo, že je sledován celkový počet zavedení stent-retrieveru a celkový počet extrakcí instrumentária (doporučeno max. 6×). Všechna centra uvedla, že je sledován stupeň dosažené reperfuze (dominantně pomocí skóre Thrombolysis in Cerebral Infarction (TICI), kdy za úspěšnou reperfúzi jsou považována skóre 2b a 3, tj. > 50 % teritoria, resp. kompletní reperfuze v případě TICI 3). Ve všech centrech jsou monitorovány peri- a postprocedurální komplikace a v 13 centrech je monitorována embolizace do nového teritoria (dle doporučení by uvedené komplikace neměly přesáhnout 15 %). V 13 centrech je standardně používáno instrumentárium k ošetření místa vpichu do femorální arterie po ukončení intervenčního výkonu (tzv. artery closure device). Po ukončení výkonu jsou ve všech centrech exportovány DSA snímky do PACS (Picture Archiving and Communication System). Čtrnáct center uvedlo, že zadává data o MT do mezinárodního registru trombektomovaných pacientů (SITS-TBY).

Trénink specialistů

V roce 2016 bylo v České republice trénováno v neurointervencích 49 lékařů a celkem 64 lékařů provádělo MT. Přitom dominující specializací lékařů byla radiologie (pouze tři lékaři byli jiné specializace – kardiologie/angiologie).

Diskuze

Dotazníkové šetření bylo vytvořeno s cílem provést první systematické zhodnocení provádění MT v iktových centrech v České republice po publikování pozitivních výsledků randomizovaných studií. Ačkoliv data získaná analýzou dotazníku jsou zatížena mnohými limitacemi (např. nelze kontrolovat skutečnou validitu odpovědí anebo zachytit veškerou variabilitu logistiky a monitorace kvality v rámci jednotlivých center), byla získána důležitá data o všech centrech provádějících MT v České republice za rok 2016.

Centra v České republice dokumentují narůstající trend v počtu provedených MT: 510 výkonů v roce 2013 vs. 1 053 výkonů v roce 2016. Při incidenci 211 ischemických iktů na 100 000 obyvatel je v České republice téměř 5 % pacientů léčeno MT [15]. Přestože zatím neexistují populační data o využití MT v klinické praxi v jiných zemích, extrapolací údajů o celkovém počtu, resp. procentu podaných IVT; lze 5 % považovat za velmi dobrý výsledek v celosvětovém měřítku [16–19]. Důvody relativně úspěšného zavedení MT do běžné klinické praxe jsou následující:

1. Česká republika měla a má organizačně dobře propracovaný systém pro IVT a počet IVT v České republice (vztažený na počet obyvatel) je jeden z nejvyšších na světě, dosahující > 15 % ze všech ischemických iktů (údaje z registru SITS).
2. Relativně vysoký počet intervenčních radiologů umožňuje zajistit nepřetržitý

provoz v režimu 24/7, což dokumentují výsledky dotazníku, a rovněž se jedná o jednu z podmínek pro zařazení do sítě center vysoce specializované péče.

Nicméně je nutné si uvědomit, že k celkově pozitivnímu výsledku (vysoký počet MT v roce 2016) nepřispěla všechna centra rovnoměrně. Počty MT v centrech podobné velikosti a se srovnatelnou spádovou oblastí byly rozdílné (17–136/centrum a rok). Do budoucna je nezbytné lépe pochopit, proč dochází k těmto rozdílům, a následně zvážit, jak tyto rozdíly minimalizovat, a centra na základě zpětné vazby motivovat ke zvyšování kvality poskytovaných výkonů (zásadně zde pomohou údaje získané z registrů SITS-TBY a REgistry of Stroke Care Quality (RES-Q).

V rámci otázek zaměřených na zobrazovací metody všechna centra v České republice uvedla, že disponují dobrým přístrojovým vybavením, což je dokumentováno velmi dobrou dostupností CT přístrojů v režimu 24/7 (všechna centra) a MR přístrojů (14/15 center). Z dostupných odpovědí vyplynulo, že doporučené multimodální zobrazovací protokoly jsou používány často. Přitom všechna centra uvedla, že hodnotí časné ischemické změny a v 8 centrech je hodnocena kolaterální cirkulace na úrovni leptomeningeálních kolaterál. Z dotazníku však nelze validně zjistit, zda jsou tyto postupy uplatňovány u všech pacientů anebo pouze u některých, jaká je forma dokumentování nálezů (např. jestli je ASPECTS a kolaterální skóre standardní a validní součástí radiologických popisů apod.). Do budoucna a v souladu s aktuálními mezinárodními doporučenými postupy ESO a AHA/ASA je nezbytná standardizace:

1. ve výběru vhodných zobrazovacích modalit v různých časových intervalech,
2. v definování protokolů provádění zobrazováních metod,
3. radiologického popisu pro všechna centra zapojená do diagnostiky a léčby akutních mozkových infarktů v České republice.

V rámci indikace MT je nezbytné provést nativní CT a CTA mozkových tepen, a to od aortálního oblouku po vertex (tj. zhodnocení rozsahu ischemických změn, přítomnosti a lokalizace uzávěru a arteriálního přístupu). Funkční zobrazení mozkového parenchymu pomocí CTP může mít svůj přínos zejména v nejednoznačných případech a hraničních indikacích MT, a to zvláště u pacientů mimo časové okno. Nicméně zatím chybí dostatek validních klinických dat o přínosu této modality v rozhodovacím procesu o indikaci MT a rovněž neexistují standardizované a validované parametry definující jádro ischemie a penumbru [20,21].

V České republice dnes chybí celonárodní standard (konsenzus odborných společností) definující způsob popisu vstupních zobrazovacích metod u kandidátů MT. Z dotazníku nebylo možné zjistit, jakým způsobem je hodnocení časných ischemických změn či kolaterálního skóre prováděno. Tedy zda se jedná o součást standardního popisu všech radiologů a zda je tento popis k dispozici ihned po provedení vstupního zobrazení (ideálně, zda je vstupní zobrazení hodnoceno radiologem a neurologem společně, kdy probíhá diskuze o indikaci pacienta k endovaskulárnímu výkonu). Rovněž doposud nejsou k dispozici údaje, jakým způsobem jsou prováděny a reportovány popisy v ostatních iktových centrech – nejen u potenciálních kandidátů MT.

Do budoucna považujeme za nezbytné:

1. konsenzem CVS ČNS a ČSIR vypracovat dokument definující standardy neurozobrazení a radiologických popisů (např. vytvořením jednotného celonárodního formuláře pro popis vstupního zobrazení mozkového parenchymu a mozkových tepen);
2. zajistit pravidelný a systematický trénink v hodnocení CT a MR ve vztahu k indikacím MT;
3. pacienty se suspekcí na uzávěr velké mozkové tepny směřovat přímo do komplexního cerebrovaskulárního centra.

Výsledný klinický stav pacientů (neurologický deficit) po IVT a MT je zásadně ovlivněn dvěma faktory: rychlostí zahájení účinné terapie (koncept time is brain) a stupněm dosažené rekanalizace, resp. reperfuze. Tyto údaje by proto měly být monitorovány, analyzovány a srovnávány na národní a mezinárodní úrovni. Bez znalostí těchto údajů totiž nelze konstatovat, že iktová péče na úrovni centra či země je dostatečně kvalitní. Z výsledků provedeného dotazníku např. vyplývá, že čas příjezd–punkce třísla nebyl v roce 2016 monitorován v jednom z oslovených center a čas příjezd–dosažení reperfuze nebyl sledován v 5 centrech [9,14]. V reálné klinické praxi a v rámci centra je velice obtížné, aby všichni členové iktového týmu měli znalosti o logistice všech pacientů. Proto je nejjednodušším řešením zadávat logistické, technické, časové a další parametry do registru. Na základě těchto údajů CVS ČNS poskytuje od poloviny roku 2016 každý měsíc všem iktovým centrům nezbytné údaje o počtu MT a základní logistice vycházející z registru SITS. Tak je systematicky monitorována kvalita péče, je umožněno srovnání a jednotlivá centra získávají potřebnou zpětnou vazbu. Validní data z registru mj. umožňují i srovnání s jinými zeměmi (podobné studie zaměřené na provádění MT proběhly na národní úrovni ve Francii a lokální úrovni v rámci Kalifornie ve Spojených státech amerických) [22,23].

Kvalita prováděných výkonů záleží rovněž na objemu, tedy počtu pacientů za dané období [24]. Do budoucna je nezbytné v rámci zvyšování erudice monitorovat počet intervenčních výkonů (a také úspěšně provedených výkonů) na jednoho lékaře [25,26].

Shrnutí

Výsledky provedeného dotazníku ukazují, že Česká republika disponuje dobrou dostupností a odbornou úrovní v rámci MT u akutního mozkového infarktu. Vzhledem k metodologii získání informací (sebehodnotící dotazník) je tyto výsledky nutné chápat s určitou rezervou a s vědomím uvedených limitací. Dotazník mj. přinesl údaje o variabilitě v počtu provedených výkonů v jednotlivých centrech za rok 2016. Základními nástroji pro další zlepšování péče musí být systematické vzdělávání a implementace systému kontroly kvality, které poskytnou zpětnou vazbu a budou motivovat lékaře k dalšímu zlepšování iktové péče.

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Annex 5

KÖCHER M., D. SANAK, J. ZAPLETALOVA, F. CIHLAR, D. CZERNY, D. CERNIK, P. DURAS, L. ENDRYCH, R. HERZIG, J. LACMAN, M. LOJIK, S. OSTRY, R. PADR, V. ROHAN, M. SKORNA, M. SRAMEK, L. STERBA, D. VACLAVIK, J. VANICEK, O. VOLNY and A. TOMEK. Mechanical Thrombectomy for Acute Ischemic Stroke in Czech Republic: Technical Results from the Year 2016. Cardiovascular and Interventional Radiology [online]. 2018, 41(12), 1901–1908. ISSN 0174-1551.

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CLINICAL INVESTIGATION STROKE

Mechanical Thrombectomy for Acute Ischemic Stroke in Czech Republic: Technical Results from the Year 2016

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Abstract

Background and Purpose Experienced multidisciplinary stroke team and well-organized hospital management are considered necessary to achieve good results after mechanical thrombectomy (MT) in acute ischemic stroke patients. We analyzed the technical results of MT performed in the Czech Republic in the year 2016 to provide relevant data for further quality improvement.

Material and Methods All centers performing MT in the CR were called for detailed technical and clinical data from year 2016, which were anonymously analyzed and relevant technical key time intervals were compared. Clinical outcomes were assessed according to the HERMES meta-analysis.

Results In the 2016, 1053 MTs were performed in the CR. Of 15 dedicated centers, the data from 12 centers and from 886 (84%) patients (49.2% males, mean age 69.8 ± 12.3 years) were analyzed. The overall median of time from hospital arrival to groin puncture (GP) was

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77 min with a range from 40 to 109 min among individual hospitals, from GP to first passage of stent retriever 20 (15–40) min and from GP to maximal reached recanalization 42 (33–80) min. The median of recanalization time was 240 (219–320) min. The recanalization (TICI 2b-3) was achieved in 81.7% of patients, 44.1% of patients had a good 3-month clinical outcome and 6.3% suffered from symptomatic intracerebral hemorrhage. Peri-procedural complications were recorded in 89 (10%) patients.
Conclusion Despite achieved good overall results, a great variability in some of the analyzed key time intervals among individual centers performing MT warrants further quality improvement.

Keywords Acute ischemic stroke · Mechanical thrombectomy · Technical results · Complications · Time intervals

Introduction

Since the positive randomized trials were published [1–5], mechanical thrombectomy (MT) became a standard treatment option in acute ischemic stroke (AIS) patients with a symptomatic occlusion of large cerebral artery in anterior circulation (AC) within first 6 h after stroke onset [6, 7]. Recently published results of the randomized trials DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-UP and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE-3 (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) showed that time window for MT may be extended beyond 6 h in patients carefully selected on the basis of the brain imaging findings and clinical deficit [8, 9].

The HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) meta-analysis showed a substantial clinical efficacy of MT [10]; however, an experienced multidisciplinary stroke team, a well-organized hospital management and good technical results are considered necessary to achieve such good clinical results. Thus, all centers performing MT worldwide have a challenge to achieve similar good technical and clinical results. The recently published Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke points out selected key time intervals and process metrics for quality improvement in endovascular therapy of AIS and recommends dedicated centers to review and analyze transparently the multidisciplinary management of endovascular treatment to identify parameters for further improvement [11].

We aimed to report the detailed technical results of MT performed in the Czech Republic (CR) in the year 2016 to provide relevant data for further quality improvement in this treatment process and establish a benchmark for future comparisons and analysis.

Methods

In our country, a two-step stroke care network was established and guaranteed by the Ministry of Health since 2011. Thirty primary stroke centers (SC) that represent the first step of the network provide essential stroke care including intravenous thrombolysis (IVT) and refer patients for MT. Fifteen secondary comprehensive stroke centers (CSC), as a second step, provide advanced and comprehensive stroke care including both endovascular and surgical treatment of ischemic and hemorrhagic stroke in "24/7" regimen [12]. Patients with stroke symptoms are transported by ambulance service to the nearest center; if it is primary SC, patients are referred to the nearest CSC immediately after a brain imaging and initiation of IVT [13].

In all centers performing MT, intervention is done by certified interventional radiologists in established multidisciplinary teams, which contain also stroke neurologists, emergency staff and anesthesiologists [13]. Interventional radiologists are certified after a two-year standardized fellowship terminated with an oral examination. The fellowship and certification are guaranteed by the Ministry of Health in cooperation with the Czech Society of Interventional Radiology.

During October 2017, all centers performing MT were called for detailed technical parameters and selected clinical data from patients treated with MT in 2016. The obtained data were collected and analyzed anonymously.

Admission clinical status was evaluated using the National Institutes of Health Stroke Scale (NIHSS) by a neurologist. All patients underwent computed tomography (CT) including CT angiography or magnetic resonance imaging (MRI) including MRI angiography of brain [13].

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Even though the recommended pretreatment ASPECT (Alberta Stroke Program Early CT) score was ≥ 6 on CT or ≥ 5 on MRI-DWI, in a patient with a score lower than 6 resp. 5, MT was not contraindicated [13]. No recommendation based on CT or MRI perfusion imaging was established for patient selection within the standard 6-h therapeutic time window.

Eligible patients were treated with IVT. Mechanical thrombectomy was performed using stent retrievers mostly. Intervention was usually initiated with a stent retriever, and if needed, a thrombus aspiration was added using a dedicated aspiration catheter. In a minority of patients, distal aspiration alone or a combination of aspiration and stent retriever was performed as the first step according to a radiologist's decision. Achieved recanalization status was assessed according to the Thrombolysis in Cerebral Infarction Scale (TICI) on the final angiogram [14].

In all patients, the occurrence of intracerebral hemorrhage (ICH) was assessed on the control CT or MRI after 24 h. Symptomatic ICH (SICH) was defined as a local remote parenchymal hematoma (type 2) or subarachnoid hemorrhage associated with at least four-point increase in the NIHSS score or leading to death [15].

Neurological deficit was evaluated using the NIHSS after 24 h and clinical outcome after 3 months using the modified Rankin scale (mRS). A score of 0–2 points was considered a good outcome.

All complications (including technical) associated with MT were recorded and collected from all affected patients. The following complications were analyzed: arterial dissection, arterial dissection with occlusion, arterial perforation, distal embolization and groin complication, which was defined as any severe hemodynamically relevant bleeding requiring either surgical or endovascular treatment.

The collected data were compared among individual analyzed centers, and selected overall results were compared with those available from the HERMES meta-analysis or from the individual positive randomized trials.

Statistical Analysis

SPSS software (version 22.0; SPSS, Chicago, Illinois) was used for statistical analysis. Fisher's exact test, Chi-square test and Mann–Whitney U test were used for comparison of selected groups. Data normality was tested using Shapiro–Wilk test. Student t-test with Bonferroni correction was used for comparisons of key time intervals among individual centers. All tests used an α-level of 0.05 for significance.

Results

In the year 2016, 1053 MTs were performed for AIS in our country. Of the 15 centers performing MT, the complete data from 12 centers and from 886 (84.1%) patients (49.2% males, mean age 69.8 ± 12.3 years) were provided for the analysis. One center did not provide the patients' data and two other centers were excluded for a substantial data incompleteness. The baseline and clinical characteristics of analyzed patients are shown in Table 1. Six hundred eight (71.0%) patients were treated with IVT prior to MT, and 277 (31.3%) patients were transported secondarily for MT from SC to the dedicated CSC. Six hundred three (68.1%) patients were treated for an occlusion of MCA, 86 (9.7%) for basilar artery occlusion (BAO), 131 (14.8%) for "T" occlusion of the intracranial part of ICA and 69 (7.8%) for a tandem occlusion (TO) (Table 1).

Overall and cumulative values of all key time intervals and clinical outcomes from all analyzed patients are shown in Table 2. The median time intervals from stroke onset to groin puncture (GP) (185 vs. 210 min, $p = 0.001$) and to the first passage of stent retriever (217 vs. 244, $p = 0.001$) were significantly longer in patients with BAO compared to those with occlusion in AC (ACO) (Supplementary online Table 1). Similarly, the median time interval from GP to a maximal achieved recanalization was longer in patients with BAO (40 vs. 50 min, $p = 0.022$) (Supplementary online Table 1). Patients with TO in AC had a significantly longer interval from GP to the first passage of stent retriever (20 vs. 31 min, $p < 0.0001$) and from GP to maximal achieved recanalization than patients with a single occlusion (40 vs. 52 min, $p = 0.0001$) (Supplementary online Table 2).

Patients who were transported secondarily from CS to CSC for MT were more frequently treated with prior IVT (77.2% vs. 68.7%, $p = 0.013$), had significantly shorter time interval from hospital arrival to GP [door-to-groin time (DGT)] (44 vs. 82 min, $p < 0.0001$) and interval from hospital arrival to maximal achieved recanalization (100 vs. 126 min, $p < 0.0001$) (Supplementary online Table 3).

Recanalization (TICI 2b-3) was achieved in 723 (81.7%) patients and complete (TICI 3) in 58.6% of our patients (Table 2). Two hundred twenty (24.9%) patients were treated under general anesthesia (GA).

A good 90-day clinical outcome (mRS 0–2) was achieved in 364 (44.1%) patients (Table 2), and no difference was found between the patients with ACO and BAO, between single occlusion (SO) and TO and between the patients primarily transported to CSC and those referred secondarily from SC to CSC (Supplementary online Table 3). Two hundred thirteen (24.0%) patients died within 3 months (Table 2). The 3-month mortality differed

Table 1 Baseline demographic and clinical characteristics of analyzed patients

Parameter	Value
N, males (%)	886, 436 (49.2%)
Age (mean ± SD, years)	69.8 ± 12.3
Admission NIHSS (median, range)	16 (1–37)
Arterial hypertension	674 (76.1%)
Atrial fibrillation	352 (39.8%)
Diabetes mellitus	239 (27.0%)
Ischemic heart disease	361 (41.0%)
Hyperlipidemia	387 (43.7%)
Smoking	182 (24.7%)
Prior ischemic stroke (*n*, %)	126 (16.4%)
Stroke in anterior circulation (*n*, %)	747 (84.0%)
MCA occlusion (*M*1 + *M*2 segment) (*n*, %)	547 (61.7%)
MCA occlusion; M1 segment (*n*, %)	484 (54.8%)
ICA "T" occlusion (*n*, %)	131 (14.8%)
Tandem occlusion (ICA + MCA) (*n*, %)	69 (7.8%)
BA occlusion (*n*, %)	86 (9.7%)
Other occlusion (ACA, PCA, VA)	45 (5.1%)
IV thrombolysis (*n*, %)	628 (71.0%)
Secondary transport for MT from SC to CSC (*n*, %)	277 (31.3%)

ACA anterior cerebral artery, *BA* basilar artery, *CSC* comprehensive stroke center, *ICA* internal carotid artery, *IV* intravenous, *MCA* middle cerebral artery, *MT* mechanical thrombectomy, *NIHSS* National Institute of Health Stroke Scale, *PCA* posterior cerebral artery, *SC* stroke center, *SD* standard deviation, *VA* vertebral artery

Table 2 Overall technical and clinical results

Parameter	Value
Interval: "stroke onset—arrival to hospital performing MT" (median, range, mean ± SD, min)	100 (0–1110) 139 ± 130
Interval "hospital arrival—GP" (median, range, mean ± SD, min)	77 (5–1975) 88 ± 89
Interval "arrival to catheterization room—GP" (median, range, mean ± SD, min)	15 (1–80) 15 ± 9
Interval "stroke onset—GP" (median, range, mean ± SD, min)	192 (56–1975) 227 ± 147
Interval "stroke onset—first passage of stent retriever" (median, range, mean ± SD, min)	220 (70–1896) 255 ± 149
Interval "GP—first passage of stent retriever" (median, range, mean ± SD, min)	20 (4–138) 25 ± 17
Interval "stroke onset—maximal achieved recanalization" (median, range, mean ± SD, min)	240 (79–1991) 281 ± 167
Interval "hospital arrival—maximal achieved recanalization" (median, range, mean ± SD, min)	122 (25–1991) 135 ± 99
Interval "GP—maximal achieved recanalization" (median, range, mean ± SD, min)	42 (9–195) 48 ± 27
Achieved recanalization (TICI 2b, 3) (*n*, %)	723 (81.7%)
General anesthesia (*n*, %)	220 (24.9%)
Symptomatic intracerebral hemorrhage (*n*, %)	56 (6.3%)
3-month mRS score 0–2 (*n*, %)	364 (44.1%)
3-month mortality (*n*, %)	213 (24.0%)

GP groin puncture, *MT* mechanical thrombectomy, *mRS* modified Rankin scale, *SD* standard deviation, *TICI* thrombolysis in cerebral ischemia scale

significantly between BAO and the patients with ACO only (45.3% vs. 23%, $p < 0.0001$) (Supplementary online Table 1).

SICH occurred in 56 (6.3%) patients (Table 2), and no difference was found between patient subgroups in the rate of SICH (Supplementary online Tables 1–3). One hundred three peri-procedural complications were recorded in 89

(10.0%) patients, and peripheral embolism was the most frequent complication (42, 4.7%). The rates of individual recorded complications did not differ between patients with BAO and ACO, with SO and TO and between patients treated primary in CSC and patients referred secondarily from SC to CSC (Supplementary online Table 4).

Comparisons of analyzed key time intervals among individual centers and with overall "national" medians are shown in Table 3 and in Supplementary online Figures 1–4. The comparison of 3-month clinical outcome among individual centers is shown in Table 4 and Supplementary online Figure 5. In four hospitals, the median of DGT exceeded significantly the overall median of 77 min (Table 3, Supplementary online Figure 1). The median time interval from GP to the first passage of stent retriever was significantly longer in two centers and significantly shorter in three centers (Table 3, Supplementary online Figure 2). In six hospitals, the median from GP to maximal reached recanalization significantly exceeded the overall median of 42 min (Table 3, Supplementary online Figure 3). The median interval from stroke onset to recanalization was significantly longer than the overall median of 240 min in three centers (Table 3, Supplementary online Figure 4). The proportion of patients with good 3-month clinical outcome was significantly lower in two centers and higher in one center in comparison with overall rate (Table 4, Supplementary online Figure 5).

Discussion

We present nationwide data containing detailed technical results of MT for AIS from the year 2016. Following recently published nationwide clinical report [16], we focused on time and quality parameters associated with the technical aspects of performed MT to establish a benchmark for future comparisons and analysis and to provide data for further quality improvement. The presented analysis involved a vast majority of treated patients in the year 2016 in CR and documented sufficiently a real clinical practice in our country.

In comparison with results reported from the HERMES analysis [10], the recanalization rate was higher in our ACO patients (81.2% vs. 71.0%, $p < 0.001$, OR 1.752, 95% CI 1.351–2.272), the number of patients with mRS 0–2 was similar (45.1% vs. 46%, $p = 0.747$) and the rate of SICH did not exceed the rate from HERMES analysis (6.8% vs. 4.4%, $p = 0.055$). Significantly higher 3-month mortality in our cohort (23.0% vs. 15.3%, $p = 0.0004$) might be related to non-selected treated population and to a higher presence of diabetes and hypertension in our patients (Table 1).

The overall achieved recanalization (81.7%) in the presented study was comparable with the rate (81.4%) from nationwide 1-year study published from Austria [17]. As similarly reported in the Austrian study, we did not find significant difference in the recanalization rate between ACO and BAO patients and patients with SO and TO (Supplementary online Tables 1, 2).

We emphasize, in accordance with the recent multidisciplinary consensus, the importance of critical review and transparent analysis of key time intervals and process metrics in each of the centers performing MT [11]. Our results showed a great variability among individual hospitals in some of the analyzed time intervals and significant differences in comparison with "national" overall medians of key time intervals (Table 3, Supplementary online Figures 1–4). We consider several possible reasons for the found variability among centers: (a) different techniques used for MT among centers; new approaches with aspiration catheters such as ADAPT technique or more complex SOLUMBRA or SAVE systems [18–20] were started to be used in some centers, (b) a different personal experience of interventional radiologists with a different treatment strategy and decisions based on a personal experience in individual centers, (c) a different local management and logistics with absence of emergency room or centralized imaging and intervention facilities in some centers. Some differences among centers might also be affected by a higher number of secondary transports for MT or unfavorable geographical location of individual centers.

The results of our study will be analyzed and discussed among members of the Executive Committees of the Czech Stroke Society and the Czech Society of Interventional Radiology. Our aim was to establish national benchmarks for individual key time intervals with an impact on centers exceeding significantly the "national medians" to improve their management and logistics of MT. Further prospective study is planned next year to compare key time intervals between both years and to assess trends in individual centers. Based on a result of this comparison and a joint decision of both societies, the Multidisciplinary Working Committee of Ministry of Health of CR may discontinue the running of individual center until a rectification as a last resort.

Due to limited provided times and technical parameters from the HERMES analysis, we were not able to compare the key time intervals. Although the interval from stroke onset to maximal recanalization seemed to be shorter in our patients (median 238 vs. 281 min), the direct comparison was not possible, because of missing mean value with standard deviation from the HERMES meta-analysis. Moreover, we consider a randomization process in trials as a factor for an obligatory delay that limits a fair comparison with non-randomized studies.

As expected, our patients with TO in AC had significantly longer time interval from GP to the first passage of stent retriever and the time interval from GP to maximal

Table 3 Comparison of key time intervals (min) among individual hospitals and with overall medians and means

	DGT interval			Groin puncture-first pass interval			Groin puncture-TICI 2b/3 interval			Stroke onset-TICI 2b/3 interval		
Center	Median	Mean ± SD	*p*	Median	Mean ± SD	*p*	Median	Mean ± SD	*p*	Median	Mean ± SD	*p*
1	75	70 ± 30	1.000	35	38 ± 21	0.072	50	57 ± 26	**0.012**	263	297 ± 147	0.088
2	85	85 ± 37	0.864	25	29 ± 19	1.000	40	46 ± 25	1.000	252	275 ± 145	1.000
3	90	108 ± 92	**0.002**	15	14 ± 6	**< 0.0001**	35	40 ± 20	1.000	220	244 ± 136	1.000
4	90	111 ± 84	**0.012**	23	25 ± 10	0.120	43	46 ± 21	1.000	252	290 ± 159	0.192
5	69	70 ± 31	0.576	21	27 ± 15	1.000	40	45 ± 27	1.000	222	242 ± 85	1.000
6	53	74 ± 63	1.000	13	19 ± 15	**< 0.0001**	38	42 ± 24	1.000	219	307 ± 225	0.540
7	76	96 ± 184	1.000	16	20 ± 13	**0.0001**	33	37 ± 18	**0.048**	230	275 ± 203	1.000
8	109	117 ± 51	**< 0.0001**	35	37 ± 15	**0.012**	55	58 ± 26	**0.012**	283	320 ± 104	**0.0003**
9	40	51 ± 32	**< 0.0001**	24	28 ± 14	1.000	40	48 ± 26	1.000	225	266 ± 171	1.000
10	87	103 ± 57	**0.048**	40	50 ± 29	**< 0.0001**	80	84 ± 41	**< 0.0001**	320	391 ± 263	**< 0.0001**
11	80	84 ± 65	1.000	19	19 ± 7	1.000	48	52 ± 27	**0.036**	265	291 ± 124	**0.036**
12	93	98 ± 44	0.168	30	36 ± 17	0.372	48	47 ± 18	**0.042**	253	265 ± 87	1.000
CR	77	88 ± 89		20	25 ± 18		42	48 ± 27		240	281 ± 167	

Statistically significant values are given in bold ($P < 0.05$)

CR Czech Republic, *DGT* door–groin time interval, *SD* standard deviation

Table 4 Comparison of numbers of performed MT and 3-month clinical outcomes among individual centers

Center	N	mRS 0–2 (*n*, %)	Median of mRS	*P*	OR	95% CI
1	42 (4.7%)	13 (31%)	3	0.191	0.643	0.330–1.253
2	71 (8.0%)	23 (35.4%)	3	0.151	0.687	0.411–1.150
3	128 (4.4%)	56 (43.8%)	3	0.567	1.115	0.767–1.621
4	74 (8.4%)	38 (51.4%)	2	0.058	1.514	0.941–2.434
5	87 (9.8%)	43 (49.4%)	3	0.132	1.401	0.902–2.178
6	52 (5.9%)	20 (39.2%)	3	0.709	0.896	0.505–1.592
7	114 (12.9%)	49 (43.4%)	3	0.698	1.081	0.729–1.603
8	46 (5.2%)	21 (45.7%)	3	0.539	1.205	0.664–2.185
9	114 (12.9%)	61 (53.5%)	2	**0.012**	1.651	1.116–2.442
10	49 (5.5%)	16 (55.2%)	2	0.242	0.695	0.377–1.282
11	78 (8.8%)	19 (37.3%)	4	**0.004**	0.462	0.271–0.788
12	31 (3.5%)	5 (19.2%)	5	**0.005**	0.276	0.105–0.725
CR	886 (100%)	364 (44.1%)	3			

Statistically significant values are given in bold ($P < 0.05$)

achieved recanalization (Supplementary online Table 2). These patients were also more frequently secondarily transported from CS to CSC for MT, were more frequently treated with IVT and were more frequently smokers (Supplementary online Table 2). Frequent smoking may be related to the presence of atherosclerosis, which led to extracranial ICA occlusion.

Patients with BAO had a significantly longer time interval from GP to maximal achieved recanalization (Supplementary online Table 1). We suggest this might be associated with a different type of thrombus and character of occlusion compared to ischemic stroke in AC. Significantly lower occurrence of atrial fibrillation in BAO patients may support our hypothesis (Supplementary online Table 1). Moreover, a different vascular approach and morphology in case of BAO might also play some role. Despite a significantly higher number of BAO patients treated in GA, no significant delay was observed in DGT compared to patients with ACO (Supplementary online Table 1).

Patients who were transported secondarily for MT from SC to CSC had significantly longer time interval from stroke onset to maximal achieved recanalization despite significantly shorter DGT in the CSC, time interval from GP to the first passage of stent retriever and to maximal achieved recanalization (Supplementary online Table 3). This finding may support the opinion that all AIS patients with a moderate or severe deficit should be transported directly to the centers performing MT despite a longer distance.

Interestingly, the rate of peri-procedural complications did not differ between the subgroup of patients with single occlusion in AC, BAO and tandem occlusion (Supplementary online Table 4), despite a prior stenting of the occluded ICA and longer time intervals from GP to the first passage of stent retriever and to maximal recanalization in the patients with TO. The total rate of complications was not provided in the HERMES meta-analysis; nevertheless, the rate of distal embolism (5.2%), arterial perforation (2.1%), arterial dissection (3.3%) and groin hematoma (0.8%) did not exceed the rates reported from the REVASCAT, MR CLEAN and SWIFT-PRIME trials [1, 3, 4].

General anesthesia (GA) was used in 24.9% of our patients, which was less frequent than reported in the MR CLEAN (37.8%) and SWIFT-PRIME (37%) trials [1, 3]. The rate of the patients on GA in our cohort may decrease to 14.3% when excluding 39 patients on GA with BAO.

A well-organized multidisciplinary team is considered essential to achieve good technical and clinical results after endovascular treatment of AIS. We suggest, in agreement with others, that certified interventional radiologists should perform MT preferably and be responsible for all technical aspects of this endovascular procedure [13, 21]. In CR since this year, newly applied interventional radiologists should be trained under a supervision of an experienced interventional radiologist also for MT and have been obligated to document a certain number of performed MT. Besides this universal certification for interventional radiology, no additional certification for interventional neuroradiology exists in our country.

Our study has several limitations. Firstly, the study design was retrospective. Secondly, the presented analysis did not include all treated patients due to the data incompleteness from two CSC and missing data from one of the centers. Thirdly, we did not collect data about "door-to-imaging" and "imaging-groin puncture" intervals, because we aimed to focus on the technical metrics of MT which are solely the responsibility of the interventional radiologist. Nevertheless, we respect the importance of these intervals for the improvement of patient logistics before MT. Thus, these parameters will be involved in further planned prospective study next year.

Only limited data comparison with the HERMES meta-analysis was performed due to a small number of provided technical parameters and time intervals. Moreover, our patients' cohort involved besides the patients with single occlusion in AC and also patients with tandem occlusion, which limits the comparison with HERMES patients.

We emphasize the importance of analysis of key time intervals related to technical aspects of MT and identification of possible time loss during the acute management of MT. The assessment of mean time intervals based on nationwide analysis allows to compare the results among the individual centers and may help to improve the management and logistics of MT. Moreover, the centers with superior results may challenge or inspire the others to shorten key time intervals. However, recently released and launched "physiology is brain" illustrates a new paradigm in acute stroke treatment with an increasing importance of collaterals, good ASPECT score and perfusion imaging; we still believe in old-known "time is brain" paradigm and consider extremely important time intervals in the management of MT to reach a clinical success and patient early recovery after AIS. Thus, all centers should continue in a strong effort to shorten the key time intervals in the management of MT.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study, formal consent is not required.

Informed Consent For this type of study, informed consent does not apply.

Consent for Publication For this type of study, the consent for publication is not required.

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