CHARLES UNIVERSITY

Faculty of Medicine in Hradec Králové

Utilization of CTA and CTP in Middle Cerebral Artery Stroke

Petra Cimflová

Autoreference of the Dissertation

Doctoral Study Programme: Radiology

Hradec Králové

2022

Dissertation thesis was written during *part-time* doctoral (Ph.D.) study programme Radiology at the Department of Radiology, Faculty of Medicine in Hradec Králové, Charles University.

Author: MUDr. Petra Cimflová
Department of Radiology, University of Calgary, Calgary, Canada
Department of Medical Imaging, St. Anne's University Hospital Brno, Brno, Czech Republic

Supervisor: Prof. MUDr. Antonín Krajina, CSc
Department of Radiology, Faculty of Medicine Charles University and University Hospital, Hradec Kralove, Czech Republic

Consultant-Supervisors: Assoc. Prof. MUDr. Kamil Zeleňák, PhD
Department of Radiology at the Jessenius Faculty of Medicine in Martin of Comenius University in Bratislava, Slovakia

Opponents: Prof. MUDr. Neuwirth, CSc, MBA
Department of Radiology, Institute of Postgraduate Medical education, Praha
Bild och funktionsmedicin Västerbotten Norrlands universitetssjukhus, Umea, Sweden

Assoc. Prof. MUDr. Václav Procházka, Ph.D., MSc., MBA
Department of Imaging Methods, University Hospital Ostrava and Faculty of Medicine, Ostrava University, Czech Republic

The defense will be held before the Commission for defenses of the OR Radiology on November 16th, 2022 at 10.00 am at the Department of Radiology, Faculty Hospital Hradec Králové.

The dissertation is available for inspection at the Study Department of the Dean´s Office, Faculty of Medicine in Hradec Králové, Charles University, Šimkova 870, 500 03 Hradec Králové (phone 495 816 134)

MUDr. Pavel Ryška, Ph.D.

Chairperson of the Commission for Dissertation Defences
in Doctoral Study Programme Radiology

TABLE OF CONTENTS

SUMMARY

Introduction: Diagnostic imaging has a crucial role in the diagnosis and therapeutic management of acute ischemic stroke (AIS). The main aim of this thesis was to further evaluate the utilization of CTA and CT perfusion (CTP) in the diagnosis and treatment decision in patients with AIS caused by the occlusion of the middle cerebral artery.

Methods: Study in *Chapter 2* evaluated the automatically derived CT perfusion lesion volumes (PLV) and hypoperfusion intensity ratio (HIR) with collateral score using multiphase CTA (mCTA) (Kruskal-Wallis, Wilcoxon rank-sum test and Spearman's rho correlation coefficients were calculated). In study in *Chapter 3*, the assessment of ischemic changes by expert reading and available automated software for non-contrast CT and CTP was compared (the sensitivity, specificity, positive and negative predictive value were calculated). In *Chapter 4,* the performance of Stroke*SENS* software tool in detection of anterior large vessel occlusions (LVO) was tested (receiver operator characteristics analysis). Study in *Chapter 5* investigated whether prediction of clinical outcome and final infarct volume can be improved by collateral status assessment on time-variant color-coded mCTA (multivariable logistic regression). The aims in *Chapter 6* were to determine if mCTA-derived tissue maps can detect medium vessel occlusions (MeVO), and predict follow-up infarct (sensitivity, specificity, and AUC were calculated for MeVO detection, concordance correlation coefficient and intraclass correlation coefficient for volumetric and spatial agreement between predicted infarcts on mCTA and CTP).

Results: In *Chapter 2*, we demonstrated mCTA collateral score corresponds with automatically-derived PLV with significant difference between good and poor collaterals. High accuracy for the assessment of ischemic changes by different CT modalities was demonstrated in *Chapter 3*. We showed in *Chapter 4* Stroke*SENS* LVO detected anterior LVO with high accuracy. *Chapter 5* demonstrated that collateral extent assessment on time-variant mCTA improved prediction of outcome and was comparable to conventional mCTA in predicting follow-up infarct volume. Study in *Chapter 6* showed mCTA tissue maps are reliable in MeVO detection and tissue fate prediction.

Conclusion: The correlation of mCTA collateral status and CTP-derived PLV suggests that PLV can be estimated by collateral grade in AIS patients. High accuracy of early ischemic changes assessment using automated software analysis encourages its use in clinical practice. The reliable performance of the software tool in anterior LVO detection further supports the use of machine learning based software tools in acute care to identify patients who can benefit from timely treatment. Time-variant mCTA is a suitable alternative to interpretate the collateral status. mCTA-derived tissue maps can be used to detect MeVO and estimate the volume of potentially salvageable tissue.

Key words: acute ischemic stroke, stroke imaging, multiphase CTA, CT perfusion, automatic software analysis, collateral score

SOUHRN

Úvod a cíle: Diagnostické zobrazování má zásadní roli v diagnostice a terapeutickém managementu akutní ischemické cévní mozkové příhody (AIS). Cílem této práce zhodnotit další možnosti využití CTA and CT perfúze (CTP) u AIS způsobené uzávěrem střední mozkové tepny.

Metodika: Studie v *Kapitole 2* hodnotila automaticky odvozené objemy CT perfúzních lézí (PLV) a hypoperfúzní koeficient (HIR) s kolaterálním skóre pomocí multifázické CTA (mCTA) (užití Kruskal-Wallisova a Wilcoxonova rank-sum testu, korelační koeficienty Spearmanova rho). Ve studii v *Kapitole 3* bylo porovnáno hodnocení ischemických změn hodnoceného experty a pomocí dostupného automatizovaného softwaru na nativním CT (NCCT) a CTP (stanovení senzitivity, specificity, pozitivní a negativní prediktivní hodnoty). V *Kapitole 4* byl testován software StrokeSENS v detekci uzávěru velkých cév (LVO) v přední mozkové cirkulaci (použita receiver operating characteristics analýza). Cílem studie v *Kapitole 5* bylo zjistit, zda lze zlepšit predikci klinického výsledku a konečného objemu infarktu na základě posouzení stavu kolaterál na barevně kódovaných time-variant mCTA (použita multivariabilní logistická regrese). Cílem v *Kapitole 6* bylo určit, zda tkáňové mapy generované z mCTA umožňují detekci uzávěrů středních cév (MeVO) a predikci infarkt na kontrolním zobrazení (stanovena senzitivita, specificita a AUC pro detekci MeVO, koeficient konkordanční korelace a koeficient vnitrotřídní korelace pro objemovou a prostorovou shodu predikovaných infarktů).

Výsledky: V *Kapitole 2* jsme prokázali, že mCTA kolaterální skóre koreluje s automaticky odvozenými PLV se statisticky významným rozdílem u dobrých a chudých kolaterál. Vysoká přesnost pro hodnocení ischemických změn různými CT modalitami byla prokázána v *Kapitole 3*. V *Kapitole 4* jsme ukázali, že software StrokeSENS detekoval LVO v přední cirkulaci s vysokou přesností. *Kapitola 5* demonstrovala, že hodnocení rozsahu kolaterálu na time-variant mCTA mapách zlepšilo predikci dobrého výsledku a bylo srovnatelné v predikci kontrolního objemu infarktu. Studie v *Kapitole 6* ukázala, že tkáňové mapy mCTA lze použít k detekci MeVO a k predikci infarktu.

Závěr: Korelace kvality kolaterál na mCTA a PLV odvozené z CTP značí, že velikost PLV může být odhadnuta ze stavu kolaterál u pacientů s AIS. Vysoká přesnost hodnocení časných ischemických změn pomocí automatizovaného softwaru podporuje jeho využití v klinické praxi. Spolehlivá detekce LVO automatickým software dále podporuje využití softwarových nástrojů v akutní péči pacientů s podezřením na AIS k identifikaci těch, kteří mohou mít prospěch z včasné léčby. Time-variant mCTA zobrazení představuje vhodnou alternativu k interpretaci stavu kolaterál. Tkáňové mapy odvozené z mCTA lze využít k detekci MeVO a k odhadu objemu potenciálně zachranitelné tkáně.

Klíčová slova: akutní ischemická cévní mozková příhoda, zobrazení u cévní mozkové příhody, multifázická CTA, CT perfúze, automatická softwarová analýza, kolaterální skóre

1. Chapter 1 - Introduction

Acute ischemic stroke (AIS) remains a worldwide major cause of disability and mortality. Approximately 7-8 million people suffer from AIS every year, out of which almost one half dies and about 25-30% of stroke survivors remain disabled in basic activities (1).

1.1 CT IMAGING IN ACUTE ISCHEMIC STROKE

Diagnostic imaging has an irreplaceable role in the diagnosis and therapeutic management of AIS. Within the framework of AIS, computed tomography (CT) is still the most widespread and used imaging method. CT represents a fast, simple, available and relatively inexpensive tool.

1.1.1 Non-contrast CT

Non-contrast CT is a crucial imaging modality in all patients with suspected AIS. It helps to rule out other pathology, such as intracranial haemorrhage or mass lesion as well as to assess the presence and extent of ischemic changes.

In routine practice, the most common way of quantifying the extent of early ischemic changes is the ASPECTS score (Alberta Stroke Program Early CT Score). Although ASPECTS shows greater inter-rater reliability for assessing early ischemic changes in the MCA territory than the previously used method of <1/3 or >1/3 MCA territory involvement (2), the ASPECTS score is still prone to subjective error and varies among readers (3).

The automatic assessment of the ASPECTS is nowadays available (i.e. e-ASPECTS Brainomix, iSchemaView RAPID ASPECTS) demonstrating high reliability when compared to the experienced readers (4,5). The main benefit of the use of automatic software tools in clinical practice is the possibility of fastening the patient triage (5).

1.1.2 CT angiography

The detection of the arterial occlusion confirms the diagnosis of AIS and the thrombus localization guide the treatment decisions. In standard CTA, a bolus of iodinated contrast is injected, and a single angiography scan from aortic arch-to-vertex is obtained. In multiphase CTA (mCTA), the same contrast bolus is used to obtain two additional series during the peak-venous and late venous phase, the latter two phases covering only the area from the skull base to the vertex (6).

Several automated standalone acute stroke software platforms for detection of large vessel occlusion are available in the clinical practice (e.g. RAPID CTA, VIZ LVO, etc.) using different artificial intelligence (AI) methods for automatic LVO detection.

In addition to localization of the occlusion, CTA also provides important information on the morphology of leptomeningeal collaterals. Standard CTA may underestimate the collateral extent as the CTA acquisition represents only a single snap-shot and the collateral anastomoses may not have been yet sufficiently opacified. The additional two phases of mCTA therefore overcomes this limitation and enable the better visualization of collaterals.

1.1.3 CT perfusion

CT perfusion (CTP) is a functional examination of the brain tissue that characterizes the state of cerebral perfusion and thus informs about its functional state. The goal of perfusion analysis in the clinical use is to quantify tissue with significant hypoperfusion which is likely to infarct if reperfusion is not achieved (ischemic penumbra) and identify tissue that is likely irreversibly infarcted (ischemic core) (7).

The essential hemodynamic parameters in CTP studies:

1. *Cerebral Blood Flow* (CBF) refers to the volume of blood flowing in a unit of brain mass during a unit of time, measured in milliliters/100 g/min (mL/100 g/min). CBF is often expressed proportionately (relative CBF) as normalized measure to a presumed normal reference region (in the contralateral hemisphere).
2. *Cerebral Blood Volume* (CBV) refers to the fraction of a tissue that is vascularized, expressed in the milliliters/100 g
3. *Mean Transit Time* (MTT) represents the average time that takes a contrast bolus to traverse the capillary bed; MTT is reported as an absolute in seconds.
4. *Time to maximum of the residual function* (Tmax) expresses the delay from the start of scan acquisition to the maximum intensity of contrast bolus in each voxel.

The tissue fate prediction is also associated with the severity of hypoperfusion (7,8). Severely hypoperfused tissue defined as Tmax delay >10s tends to progress more rapidly that the tissue with better residual perfusion through collateral flow. The severity of hypoperfusion can be quantified by the hypoperfusion intensity ratio (HIR), which represents the proportion of Tmax >6s perfusion lesion with Tmax >10s perfusion lesion (8).

1.2. CURRENT STATE OF IMAGING IN ACUTE ISCHEMIC STROKE DIAGNOSIS AND TREATMENT DECISION

The indication of the particular CT modalities is currently based on the time from the symptom onset. In order to administer intravenous thrombolysis within 4.5 hours of onset, non-contrast CT scan is required to rule out intracranial hemorrhage or other non-vascular pathology (e.g. tumor). Beside excluding the hemorrhage, non-contrast scan is used to detect early ischemic changes. CTA is used not only to confirm the AIS by detecting the arterial occlusion, but it is also highly recommended in patients indicated for mechanical thrombectomy to evaluate the extracranial vascular anatomy.

CTP scan is primarily beneficial in patients presenting between 6 and 24 hours from the symptom onset or in cases where the time of onset is unclear. CTP enables to identify patients with potentially salvageable ischemic penumbra. Another advantage of CTP even in early stages is the identification of perfusion lesion (hypoperfused area) in situations when patients have small neurological deficit or when stroke-mimics are suspected.

1.3 FUTURE DIRECTIONS

The numerous different software solutions for image analysis and different imaging modalities are currently used in acute stroke imaging, The expanding availability of the automatic software analysis enables fasten the patients' triage in the acute management and reduce the inter-rater

variability.

Novel visual aids, such as time-variant mCTA maps or mCTA-derived CTP-like maps are promising tools that have been recently introduced. Time-variant (color-coded) mCTA display format encodes vascular information from all mCTA phases into a single color-coded map, combining the indicator effect of color with the technical advantages of mCTA (9). mCTA-derived CTP-like maps are based on the machine learning technique to estimate infarct core and ischemic penumbra in patients with AIS (10).

1.4 AIMS OF THE THESIS

Despite the known applications of CTA and wide use of CTP as a part of the standard stroke management protocol, the main aim of this thesis was to further evaluate the utilization of these imaging modalities in the diagnosis and treatment decision in patients with acute ischemic stroke caused by the occlusion of the middle cerebral artery.

The correlation of the leptomeningeal collateral grading using mCTA and perfusion lesion volumes derived from the automatic CTP analysis was investigated in **Chapter 2**. In **Chapter 3**, we investigated the accuracy of different CT modalities including also automatically-derived CTP maps in the assessment of the early ischemic changes and their accuracy for the final infarct prediction.

The machine learning based software tool for automated ICA and MCA occlusion detection in patients with suspected acute stroke using was validated and its high accuracy was demonstrated (**Chapter 4**). **Chapter 5** discusses the utility of time-variant mCTA maps in the prediction of the clinical outcome and final infract volume compared to the conventional mCTA collateral grading. In **Chapter 6** investigates the accuracy of medium vessel occlusions (MeVO) on mCTA-derived tissue maps.

In **Chapter 7**, the general implications of the findings in this thesis and directions for the future research are discussed.

2. Chapter 2 - Correlation of the multiphase CTA collateral score and the automatically-derived CT perfusion volumes

2.1 INTRODUCTION

The quality of the leptomeningeal collateral flow in acute ischemic stroke due to the large vessel occlusion in the anterior territory is associated with patients' clinical outcome (11,12), infarct growth and final infarct volume (13–15), and hemorrhagic transformation (16).

Previously published studies (17–19) comparing the collateral flow on CTA and CTP were predominantly focused on the associations related to the good collaterals. In the original publication by Menon et al. (6), in which the authors introduced mCTA, they highlighted a possibility of the underestimation of the leptomeningeal collateral flow on the standard (single-phase) CTA. That means that also intermediate collaterals (represented by delayed filling of the collaterals by 1 phase and some decrease in their extend or 2 phase delay but no decrease in extend compared to the unaffected side) should still be considered sufficient rather than poor. Therefore, the aim of the study was to evaluate perfusion lesion volumes (PLV) for each collateral grade and identify automatically derived CTP parameters associated with poor collateral flow as defined by Menon et al. (6)

2.2 MATERIALS & METHODS

Patient selection

Retrospective review of imaging data of consecutive patients who underwent mechanical thrombectomy at the comprehensive stroke center during the period from Jan 2016 to Dec 2020 was performed. Patients with intracranial terminal internal carotid artery occlusion (ICA) and middle cerebral artery occlusions (M1 and proximal M2 segments) with available baseline imaging data including mCTA and CTP were included. Multiphase CTA is used as a stroke imaging standard at our center since 2013, and all patients with symptoms of AIS and no history of contrast allergy routinely undergo NCCT, mCTA and CTP in our institution.

Imaging protocol

Multiphase CTA consists of three scanning phases after the contrast media injection (60ml of iodine contrast agent power-injected at 5ml/s followed by a saline chase of 40ml at 5ml/s) with a 0.625mm section thickness. The first phase from the aortic arch to the cranial vertex was followed by two additional phases from the skull base to the cranial vertex with a delay allowing the table repositioning between particular scanning phases and resulting in the performance of each phase 8s apart (6).

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.

Image processing

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 presumed ischemic core (defined as a relative regional CBF <30%) (20) and volumes of hypoperfused tissue with Tmax delay of >4s, >6s, >8s, and >10s.

Image review

The quality of leptomeningeal collaterals was assessed according to the original collateral score introduced by Menon et al. (6) by an experienced reader blindly to the patients' history and CTP. The collaterals were trichotomized into good (score = 4-5), intermediate (score = 2-3), and poor (score = 0-1). The data regarding particular CTP volumes were extracted independently.

Statistical Analysis

Clinical and imaging baseline characteristics were summarized using descriptive statistics. PLV parameters were defined as Tmax delay >4s, >6s, >8s, >10s, CBF<30%, and HIR. These parameters were compared across the collateral score categories using Kruskal-Wallis test and Wilcoxon rank-sum test. Spearman's coefficients were used to quantify correlations between the extent of collaterals and PLV or HIR. The cut-off values and their sensitivity and specificity for poor collaterals were calculated from area-under-the-curve of receiver operating characteristic curve analyses. Sensitivity analysis was performed for a subgroup with terminal ICA and M1 MCA occlusions only. All analyses were performed in Stata 16.1 (StataCorp LLC, College Station, TX, USA).

2.3 RESULTS

Mechanical thrombectomy was performed in 341 patients during the selected study period. Forty patients with the posterior circulation occlusions, 9 patients with isolated cervical ICA occlusion or ICA dissection, and 142 patients with no CTP baseline imaging were excluded. Additionally, 3 patients with poor CTP quality resulting in uninterpretable CTP maps were excluded. Data from 147 were analyzed, out of which 69 (44.2%) were women. The mean age was 71±14 years, median baseline NIHSS was 16 [interquartile range (IQR) 12-19] and the median baseline ASPECTS was 8 (IQR 7-9). The median time from the onset to CT was 83 min (IQR 60-169 min), all included patients had the baseline CT <6h from the symptom onset. Leptomeningeal collaterals were scored as good in 63 (42.9%), intermediate in 73 patients (49.7%), and poor in 11 patients (7.5%). 20 patients had terminal ICA occlusion, 96 patients (65.3%) had M1-MCA occlusion and 31 (21.1%) patients had M2-MCA occlusion. The collateral status differed between the occlusion sites (p=0.002) with the better collateral score in M2 occlusions [good collaterals in 21/31 (67.7%) in M2-MCA occlusions compared to 38/96 (39.6) and 4/20 (20%) in M1-MCA and terminal ICA occlusions, respectively].

Collateral score and hypoperfusion volumes

The PLVs significantly differed between good and poor collateral status in Tmax >10s, Tmax >8s, Tmax >6s, and CBF <30%; between good and intermediate collaterals in all evaluated perfusion parameters. The PLVs were similar between intermediate and poor collaterals except for the PLV from CBF <30%, **Table 2.1**.

Similar to perfusion lesion volumes, HIR was increasing with decreasing collateral grade and was significantly different between good and poor collateral grade ($p<0.001$) and between good and intermediate collateral grade ($p <0.001$). The Spearman's rho demonstrated significant correlations between the collateral score and the perfusion lesion volumes and HIR, with the lowest coefficients for Tmax >10s ($\rho=-0.50$) and HIR ($\rho=-0.47$).

Table 2.1. Hypoperfusion volumes in different collateral grades correlation.

Perfusion parameter	Hypoperfusion volumes (ml), median (IQR)			
	Good collaterals n=63	Intermediate collaterals n=73	Poor collaterals n=11	p-value*
Tmax >10s	36 (11 – 56)	80 (57 – 110)	125 (59 – 149)	<0.001
Tmax >8s	61 (29 – 90)	110 (94 – 138)	156 (81 – 172)	<0.001
Tmax >6s	107 (59 - 141)	152 (127 – 210)	185 (89 – 216)	<0.001
Tmax >4s	187 (126 – 282)	246 (198 – 316)	262 (157–350)	0.002
CBF <30%	7 (0 – 19)	25 (12 – 40)	65 (33 – 103)	<0.001
HIR	0.33 (0.19-0.49)	0.52 (0.35-0.65)	0.63 (0.48-0.74)	<0.001

* Derived from Kruskal-Wallis test
Note: HIR – hypoperfusion intensity ratio, IQR – interquartile range

Optimal Cut-off values to representing poor collaterals
The highest AUC=0.75 for the cut-off value representing poor collaterals was shown for CBF <30% with the cut-off value of 31ml and sensitivity and specificity of 0.82 and 0.73, respectively, followed by Tmax>10s and HIR.

Sensitivity analysis
Due to the significant difference in the collateral score based on the occlusion site, the sensitivity analysis was performed after excluding patients with M2-MCA occlusions.

Compared to the main analysis, the significant difference in perfusion lesion volumes was also observed between good and poor collateral grades when perfusion lesion volume was defined as Tmax >10s, Tmax >8s, and CBF <30% ($p<0.001$), between good and intermediate collaterals in all evaluated perfusion parameters (p-value: <0.001-0.02), and between intermediate and poor collaterals only when perfusion lesion was defined as CBF <30% ($p=0.03$). The Spearman's rho demonstrated direct correlation of the collateral score and the perfusion lesion volumes and HIR, with the strongest negative correlation for CBF <30% ($\rho=-0.46$), Tmax >10s ($\rho=-0.43$) and HIR ($\rho=-0.43$).

2.4 DISCUSSION

We demonstrated that decreasing collateral score assessed on multiphase CTA inversely correlates with increasing perfusion lesion volumes with significant difference of PLV between good and poor collaterals, which is in concordance with the previous studies (17–19). As majority of smaller hospitals and primary stroke centers do not routinely use CTP, our findings suggest that evaluation of the collateral status can also provide estimation of the ischemic core volume and severely hypoperfused tissue.

Patients with poor collaterals had significantly larger ischemic core volumes defined as

CBF <30% when compared to patient with good and intermediate collaterals and also had significantly larger areas of severe hypoperfusion defined as Tmax >10s compared to the patients with good collaterals. This association was reflected in the highest Spearman's rho correlation coefficient shown for Tmax >10s and for HIR, the known factor associated with infract growth and worse clinical outcome (8).

Although CBF <30% did not show the strongest correlation with the collateral grading in the whole dataset, the correlation increased when only patients with terminal ICA and M1-MCA occlusions were involved. This might be explained by the additional collateral flow via patent ipsilateral MCA branches in patients with M2 occlusions and therefore smaller areas with significantly decreased cerebral blood flow.

We observed that poor collaterals were best represented by CBF <30% of >31ml identifies patients with the sensitivity and specificity of 0.82 and of 0.73, respectively, while Potreck et al. (17) reported that CBF <30% perfusion lesion volume of <14ml identified patients with good collaterals with sensitivity of 0.72 and specificity of 0.82. Accordingly, the cut-off volume of 114ml associated with poor collaterals was identified for Tmax >10s in our study with the sensitivity of 0.64 and sensitivity of 0.82, while cut-off value of 53ml for Tmax >10s demonstrated association with good collaterals with the sensitivity of 0.64 and specificity of 0.80 in the work by Potreck et al. (17) These findings are complimentary to each other and provide further insight on the correlation of particular grades of collateral score and perfusion parameters.

Findings of this study supports the paradigm that the CT perfusion is not necessary in patients presenting during the first 6 hours from the symptom onset while the expected ischemic core (standardly defined as CBF <30% (7)) remains relatively small even in patients with poor collateral flow. However, the fact that the severely hypoperfused area defined as Tmax >10s was larger >100ml in patients with poor collaterals enhances the need for ultrarapid treatment in these patients as the large area of the brain is critically hypoperfused in contrast to the patients with good or intermediate collaterals, where the median of severely hypoperfused volumes were 36ml and 80ml, respectively.

Our study has several limitations. This was a single center retrospective study including patient who underwent mechanical thrombectomy, therefore there is a potential selection bias of patients with higher baseline ASPECTS and better collateral flow. The patients with poor collateral flow represented only 7.5% of the dataset which may affect the validity of the results. Second, the collateral grades were assessed visually by one reader which may introduce some level of subjective bias despite the high expertise of the reader.

2.5 CONCLUSION

This study demonstrates that mCTA collateral score correlates well with automatically-derived perfusion lesion volumes with a significant difference of PLV between good and poor collaterals. These findings suggest that evaluation of the collateral status on mCTA can provide an estimation of the ischemic core volume and severely hypoperfused tissue.

Chapter 3 - Detection of ischemic changes on baseline multimodal computed tomography: expert reading vs. Brainomix and RAPID software

3.1. INTRODUCTION

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.

3.2 MATERIALS & METHODS

Patient selection

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. 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.

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. (2) previously, blind to the results of the e-ASPECTS analysis, as well as to other baseline imaging modalities and follow-up NCCT. Automatic segmentations of ASPECTS regions on e-ASPECTS derived scans were visually checked to avoid any severe inaccuracy. CTP maps were superposed on the CT-ASPECTS template and visually assessed by an experienced reader. 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. The reader was blind to findings on NCCT. The final infarction was assessed on a 24-hour follow-up NCCT.

Statistical Analysis

Clinical and imaging baseline characteristics were summarized using descriptive statistics. The accuracy, sensitivity, specificity, PPV and NPV were calculated for particular ASPECTS regions on 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.

3.3 RESULTS

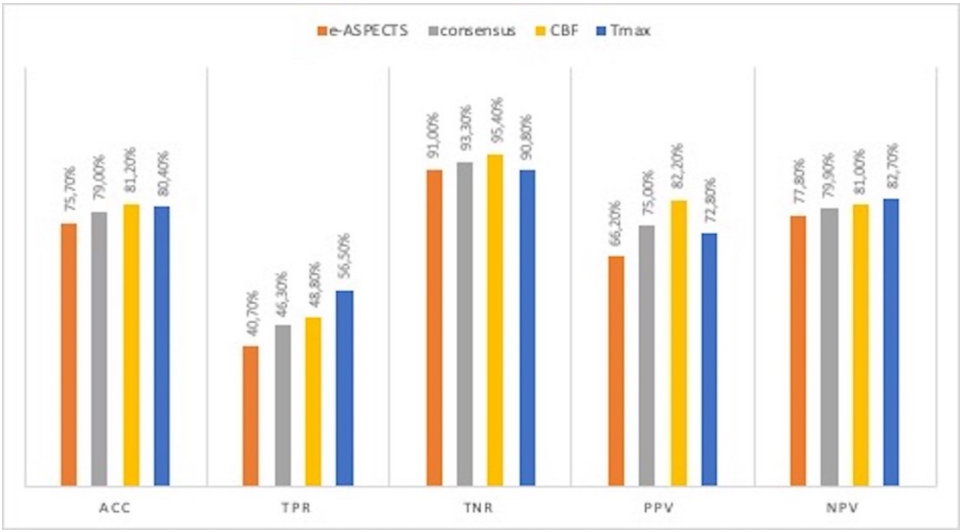
Baseline scans of 263 patients were retrospectively reviewed; 16 patients with intracranial hemorrhage and 166 patients with either negative findings on all imaging modalities or missing follow-up imaging were excluded. Overall, 81 patients met all the criteria and were included into the analysis. Mean 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%).

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 3.1.

Based on the Bland-Altman plots analysis, 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.

Figure 3.1. Accuracy, sensitivity, specificity, positive predictive value, negative predictive values 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

3.4 DISCUSSION

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.

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. Tmax delay >10s was studied previously – the association of large Tmax>10s lesion and malignant MCA profile was showed in previous studies (21,22). 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 (3,23–25) and these changes could be easily assessed on the derived perfusion maps from RAPID analysis.

The Blant-Altman plots showed the lowest difference in baseline ASPECTS and follow-up ASPECTS for Tmax>10s. 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 are aware of some limitations of this study. First of all, this was a single center observational study and patients were not selected according to the recanalization rate. We also did not focus on the correlation of ASPECTS and final clinical outcome, as this relationship has been studied elsewhere (26). The main purpose of this work was to evaluate the accuracy of ASPECTS assessment on baseline multimodal imaging.

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. This potential pitfall highlights the necessity of a visual control of CTP derived maps with NCCT or other available imaging.

3.5 CONCLUSION

Our study demonstrated high accuracy for the evaluation of early ischemic changes by different CT modalities with the best accuracy for CBF<30% and Tmax>10s. The use of automated software in everyday clinical practice has a potential to improve detection of extent of early ischemic changes.

Chapter 4 - Validation of a machine learning software tool for automated large vessel occlusion detection in patients with suspected acute stroke

4.1 INTRODUCTION

Patients with acute ischemic stroke due to large vessel occlusions (LVO), on average, may account for around 15-20% of all acute ischemic stroke patients (27). However, LVO strokes contribute to 90% of stroke mortality and severe clinical disability if left untreated (28).

Contrast-enhanced CT Angiography (CTA) has been widely adopted as the imaging standard for LVO detection in order to identify eligible patients for endovascular treatment (29–31). Since any delay in the treatment of patients with LVO directly affects patient outcomes (32), automated detection and notification of suspected LVO can help improve patient outcomes by directly reducing time to diagnosis and clinical decision making (31).

Stroke*SENS* LVO (Circle Neurovascular Imaging, Calgary, Canada) is a computer-aided triage and notification tool which utilizes machine learning to automatically detect LVO on CTA head images. The aim of this retrospective cohort study was to evaluate the software's performance in LVO detection, when compared to a neuroradiologist expert consensus assessment on imaging data from a large multi-center image database.

4.2 METHODS

Software validation dataset

The data was independent of the development dataset and was retrospectively selected from the following studies, namely, ESCAPE-NA1 (33), ALIAS (34), TEMPO-1 (35) and PREDICT (36). Inclusion criteria for the test set included subjects aged 18 years or older, who underwent baseline CTA imaging for acute stroke with image slice thickness between 0.5 mm to 2.5mm. The imaging data for the test set were acquired from multiple CT scanner models, manufactured by four different CT scanner vendors (GE, Siemens, Philips, Toshiba), as well as from multiple hospital sites and geographies. Scans determined to be technically inadequate (e.g., invalid DICOM image or inappropriate head coverage or no contrast) or with significant patient motion were excluded.

Random selection with purposive sampling was performed to achieve balanced number of LVO and other/no occlusion cases, and to ensure representation of cases acquired on multiple scanner manufacturers.

Expert-consensus was used as ground truth to establish the reference dataset labels. Three board-certified neuroradiologists (with >5 years of experience in stroke imaging) independently read all CTA images. A LVO scan was defined as containing an ICA or M1 MCA occlusion. A other/no occlusion scan was defined as any scan that does not contain an LVO, i.e., it may either had other more distally located intracranial occlusions or no occlusions at all. The readers interpreted the scans blinded to any clinical information. Consensus was determined when at least two of three readers agreed on the presence or absence of LVO. This study was approved by the University of Calgary Conjoint Health Research Ethics Board.

Statistical analysis

Baseline characteristics of patients with LVO vs. other/no occlusion were compared using a

chi-square test or Wilcoxon rank-sum test as appropriate. Expert reads on presence or absence of LVO was considered as the ground truth. Software performance for LVO detection was assessed using ROC analysis, reporting area under the curve (AUC), sensitivity, and specificity. The level of softmax cross entropy was used to calculate the AUC.

Subgroup analyses were performed to evaluate software performance in detection of M1 and ICA segment occlusions separately. Software performance was also tested on data stratified by patient sex (female versus male), age (<70 years or ≥70 years or), slice thickness (<1.0 mm or ≥1.0 mm), kilovoltage tube peak (<120 kVp or ≥120 kVp) of the scan, and scanner manufacturer (GE Medical, Siemens, Philips, Toshiba). As no cases with ICH were used for the development, a sensitivity analysis to evaluate an impact of the ICH presence on the software performance was performed.

Additionally, the mean, the maximum and the minimum processing times for positive cases (both true positive and false positive) were reported as a representative measure of time-to-notification (representing the time from the moment the scan is received in Stroke*SENS* to the notification send to the end-user). No imputation was performed for missing data since there were no missing data. Data analysis was performed using Stata 16.1 (Stata LLC Corp).

4.3 RESULTS

Out of 2779 eligible stroke cases, 1205 cases with identified baseline CTA and initial core lab reading were included into the preliminary dataset and 400 randomly selected cases (217 allocated to LVO cohort and 183 allocated to other/no occlusion cohort) were included in the test set.

The distribution of intracranial occlusion site in patients with LVO was terminal ICA (35.5%, n=77) and M1 MCA (64.5%, n=140). In the patients without LVO, there were 183 scans with either no occlusion (21.3%), a more distally located MCA occlusion (15.8%), or an occlusion in the posterior circulation (2.7%). The intracranial haemorrhage was present in 110 cases (60.1% of other/no occlusion cohort).

Of the 217 LVO cases evaluated, 194 (89.4%) were correctly identified as LVO by the software. Of the 183 other/no occlusion cases, 23 (12.6%) were incorrectly identified as LVO by the software. The sensitivity and specificity for LVO detection were 0.894 (95% CI: 0.854–0.932) and 0.874 (95% CI: 0.817–0.919), respectively, and the AUC was 0.939 (95% CI: 0.915–0.962). In analysis stratified by occlusion location, patient sex, age, slice thickness, kVp and scan manufacturer, and presence of hemorrhage the sensitivity, specificity, and AUC ranged from 0.843–0.945, 0.83–1.0, and 0.924–0.970, respectively.

The mean processing time for the sum of 217 true and false positive cases was 44.5 seconds (standard deviation ± 11 seconds), the minimum time was 18.4 seconds, the maximum time was 77.9 seconds.

4.4 DISCUSSION

In this study, we test the ability of Stroke*SENS* LVO in detecting LVO of the anterior circulation automatically in patients presenting with acute stroke. The accuracy and speed of detection of the software in a large dataset from multiple centers and geographies, using a variety of vendor machines and protocols for CTA image acquisition supports the generalizability of the

software's use in routine clinical practice.

The test set in this analysis was sampled to include a higher prevalence of common pathologies (i.e., ICH, distal occlusions, and posterior circulation occlusions) than is typically encountered in consecutive suspected acute stroke cases in the anterior circulation. The objective of the purposive sampling was to test the model's diagnostic performance in a dataset with a large representation of less straightforward cases (i.e. ICH & "other" occlusions) that are expected to be encountered by the algorithm in the clinical practice. A high proportion of hemorrhagic scans in the other/no occlusion cohort was included in order to test the consistency of the software's performance in LVO detection and verified the consistency of the tool.

Automated software systems utilizing AI for detection of stroke signs can potentially accelerate the triage, diagnosis and treatment initiation of stroke patients significantly (37). A recent study showed that utilizing an automated LVO detection software together with a notification system resulted in an average reduction of 22.5 minutes in triage and transfer times between the spoke primary stroke center and the hub comprehensive stroke center (38). A tool for automated LVO detection and notification that would streamline the clinical workflow and aid in accurate and timely patient selection for rapid EVT at spoke hospitals. The Stroke*SENS* LVO showed excellent performance in speed of potential notification with a mean processing/notification time of 44.5 seconds in this study. Although a short processing time is a promising feature, time for data transfer from the CT machine to the processing computer needs to be evaluated in the real-world.

This study has some limitations. First, the current version of the software has been developed to identify only LVOs in the anterior circulation and its primary evaluation was therefore focused only on detection of such LVOs. With increasing evidence of endovascular treatment benefit in more distally located occlusions and occlusions in the posterior territory, further software development is warranted to reliably identify such intracranial occlusions. Second, the software performance was evaluated in a retrospective fashion on data from clinical studies that may have excluded patients with stroke mimics and other non-stroke pathologies that are detected routinely in real life practice. Our study dataset consisted of an artificially high LVO prevalence (54%) as we optimized the model with as many LVO cases as possible while matching those with an equal number of examples of other/no occlusion findings. The real-world LVO prevalence is approximately 15%-30%, therefore, the evaluation of the software performance in real-world data is warranted. The Stroke*SENS* LVO's performance in LVO detection and potential speed of notification in this validation dataset will need to be supported by tests in real life conditions done in a prospective manner. Such studies are planned. Finally, the impact of tools such as Stroke*SENS* will need to be compared with current standard workflow in a randomized manner for us to understand the true benefit of such tools on the population of acute stroke patients.

4.5 CONCLUSION

Automated LVO detection and notification can aid in acute stroke management by quickly and accurately detecting patients with LVO who may likely require immediate medical attention and benefit from EVT. However, a further development including the full range of clinically relevant intracranial occlusions is as well as prospective studies exploring the impact of the software tools on acute stroke workflow and patient outcomes is warranted.

5. Chapter 5 - Utility of time-variant multiphase CTA color maps in outcome prediction for acute ischemic stroke due to anterior circulation large vessel occlusion

5.1 INTRODUCTION

Acute ischemic stroke (AIS) due to large vessel occlusion (LVO) is a highly time-critical disease. The most commonly used imaging techniques to identify irreversibly damaged tissue are CT perfusion (CTP) and multiphase CTA (mCTA). Both techniques have their advantages and disadvantages: CTP maps can be quickly and easily interpreted as the color-coded display format is a clear visual indicator of pathology. On the other hand, CTP is susceptible to patient motion and post-processing artifacts. mCTA is more robust against patient motion, and requires less contrast and radiation dose. However, the standard display format of mCTA consists of 3 separate gray-scale images of the cerebral vessels, and evaluating the collaterals requires the reader to assess all three of them simultaneously. The interpretation of mCTA therefore requires some degree of experience. The color-coded mCTA display format was recently described, in which all 3 mCTA series are consolidated in a single color-coded map, thereby potentially facilitating and improving mCTA interpretation (9).

The purpose of this study is 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.

5.2 MATERIALS & METHODS

Patient population

Patients from Prove-IT study (10) with anterior circulation LVO (internal carotid artery, M1 or proximal M2 occlusions) were included in this study. Patients in which baseline mCTA images were incomplete or not interpretable were excluded.

Image interpretation

All images were assessed in a consensus read (by a neurologist and neuroradiologist). ASPECTS was scored on 5 mm reconstructed axial unenhanced NCCT images. Occlusion site determined on axial mCTA MIP images and was reported as either terminal internal carotid artery, M1 segment or proximal M2 segment. The delay and extent of collateral filling was graded on axial MIPs of the conventional mCTA phases. The collateral grades were trichotomized as good, intermediate and poor. Both delay and extent of collateral filling were graded on a trichotomized scale on axial time-variant color-coded mCTA MIPs. Final infarct volumes were measured by summation of manual planimetric demarcation of infarct on axial NCCT or DWI-MRI follow-up imaging at 24 hours.

Statistical analysis

Patient baseline characteristics were described using descriptive statistics. Uni- and multivariable logistic regression was used to determine the association of conventional and color-coded collateral scores and a) good outcome, defined 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/above the median infarct volume in the study sample). Information loss across models was compared using the Akaike and Bayesian information criterion (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. Inter-rater agreement was assessed using the Kappa statistic. 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.

5.3 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).

Overall, 53.3% (152/285) patients achieved a good outcome at 90 days. Color-coded mCTA grading of collateral extent had lower odds for prediction of good outcome at 90 days compared to conventional collateral score [adjusted odd ratio (adjOR) 0.53; 95% confidence interval (CI) 0.36 – 0.77 versus adjOR 0.72; 95% CI 0.48 – 1.08]. Color-coded mCTA grading of collateral filling dynamics had higher odds than conventional collateral grading (adjOR 1.30; 95% CI 0.88 – 1.95 versus adjOR 0.72; 95% CI 0.48 – 1.08).

Infarct volume was available for 93.0% (265/285) patients. Median final infarct volume was 12.6 ml (IQR 1.7 – 49.2). Color-coded mCTA grading of collateral extent had similar odds in prediction of follow-up infarct volume compared to conventional collateral score (adjOR 2.67; 95% CI 1.80 – 4.0 versus adjOR 1.84; 95% CI 1.21 – 2.79). Color-coded mCTA grading of collateral filling dynamics had lower odds than conventional collateral grading (adjOR 1.21; 95% CI 0.83 – 1.78 versus adjOR 1.84; 95% CI 1.21 – 2.79).

Inter-rater agreement for color-coded grading of collateral filling dynamics and collateral extent was substantial (Kappa = 0.69 and 0.74 respectively).

5.4 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) inter-rater 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 (13). 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.

The current study relied on visual assessment of collaterals, which will always be subject to some degree of inter-rater variability. Automation of collateral scoring could mitigate this problem, but the automated assessment would have to be available instantaneously. Software to generate time-variant mCTA maps 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 is routinely available, particularly for less experienced readers.

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 occurred after treatment in the 3-month follow-up period have influenced the association with clinical outcomes, while the efficacy of treatment (either EVT or intravenous alteplase) might have influenced the association of collateral grade and final infarct volumes, although the latter two points would in theory affect both conventional and color-map based collateral grading.

Our study has several limitations: First, assessing infarct volume 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 (16). Thus, no randomized diagnostic trials have so far been conducted for any acute stroke imaging paradigm and we suspect that this will remain true in the near future as well. Sixth, the current GE FastStrokeTM Software does not allow the user to change the color-coding scheme; this might be confusing for some users who are used to different color schemes and is something that could be improved on in subsequent iterations of the software.

5.5. CONCLUSION

In this study, collateral extent, assessed on time-variant mCTA maps improved prediction of good outcome and has similar utility in predicting follow-up infarct volume compared to conventional mCTA collateral grading.

6. Chapter 6 - Multiphase CTA-derived tissue maps aid in detection of medium vessel occlusions

6.1 INTRODUCTION

Large vessel occlusions (LVOs) constitute only 10-30% of all AIS cases; 25-40% are caused by so-called medium vessel occlusions (MeVOs), which are defined as occlusion of the M2, M3, A2, A3, P2, or P3 segments with disabling deficits (39). Due to the smaller caliber, varied vascular anatomy, and more distal location compared with LVOs, MeVOs can be challenging to diagnose on imaging. Indeed, MeVOs are approximately five times more likely to be overlooked compared to LVOs (40).

Recently, mCTA-derived tissue maps with color indicator effect, analogous to CTP perfusion maps, were developed using machine learning methods and were shown to be able to predict infarct core, penumbra, and perfusion status with comparable accuracy to CTP (41). However, the majority of included images were from patients with LVOs; it currently remains unclear whether mCTA-based tissue maps are capable of aiding in the detection of MeVO stroke.

We sought to determine the accuracy of mCTA-derived tissue maps for the MeVO detection. Additionally, we quantitatively compared mCTA-based core and penumbra maps to CTP maps in their ability to predict final infarct volume in patients with definite MeVOs.

6.2 MATERIALS & METHODS

Study participants

Data used were from the PRove-IT study, a prospective multicenter study of AIS patients undergoing baseline non-contrast CT (NCCT), single-phase CTA, mCTA, and CTP. In this case-control study design, we included 116 patients, 58 with AIS due to MeVO and 58 with AIS due to non-MeVO (49 LVOs, 5 with no detectable occlusions, and 4 with occlusions of the vertebrobasilar circulation).

Image processing

First, skull stripping of the NCCT and mCTA images was performed (42). The aligned 3-phase CTA images were registered onto NCCT images using affine registration. We then used machine learning models to generate mCTA derived tissue maps for the patients with reperfusion (mTICI 2b/2c/3, core prediction) and without reperfusion (mTICI 0/1/2a, penumbra prediction), respectively (41).

CTP studies were processed using delay-insensitive deconvolution software (CT Perfusion 4D, GE Healthcare, Waukesha, WI). Absolute maps of CBF, CBV, and Tmax were generated. Time-dependent Tmax thresholds were used to generate baseline CTP thresholded maps, defined as CTP predicted infarct volume (43).

One radiologist and one stroke neurologist assessed the source baseline mCTA images for the occlusion location, if any. These were considered the standard reference of expert reads. Two radiologists manually delineated the infarct region on follow-up diffusion weighted (DWI)/NCCT imaging.

Qualitative image analysis for MeVO detection

Two radiologists independently assessed the mCTA-derived tissue maps of 116 AIS cases (58 due to MeVO, 58 due to non-MeVO) for the presence of MeVO (binary yes/no). The occlusion location was estimated based on the hypoperfusion pattern and scored as ICA, M1 MCA, anterior M2 MCA, posterior M2 MCA, M3 MCA or more distal segments, anterior cerebral artery (ACA), posterior cerebral artery (PCA), no occlusion, or "other" (e.g., occlusion of the vertebrobasilar circulation). Sensitivity, specificity, and AUC for detection of MeVO were estimated in comparison to the reference standards of 1) expert readings of the baseline CTA and 2) CTP-based Tmax maps, as read in a separate reading session. Interrater agreement was estimated using unweighted Cohen's kappa.

Volumetric and spatial analyses of mCTA-derived tissue maps

Volumetric agreement between mCTA tissue maps and CTP maps for core and penumbra volumes was assessed using concordance and intraclass correlation coefficients (CCC and ICC, respectively). The mean differences and limits of agreement (LoA) were illustrated using Bland Altman plot analysis. Spatial agreement between the two volumes was assessed using Dice Similarity Coefficient (DSC). Absolute volume agreement between mCTA predicted follow-up infarct/CTP predicted follow-up infarct and the reference standard (true follow up infarct) was reported using CCC and ICC.

6.3 RESULTS

A total of 116 cases were included in this study, 58 with MeVO (23 occlusions of the M3/4 segment of the MCA, 22 of the posterior M2 segment of the MCA, 5 of the anterior M2 segment of the MCA, 2 of the A2/3 segment of the ACA, and 6 of the P2/3 segments of the PCA) and 58 with non-MeVO (7 occlusions of the ICA, 42 occlusions of the M1 segment of the MCA, 4 occlusions of the vertebrobasilar circulation, and 5 with no occlusion).

Feasibility of mCTA-based MeVO detection

In this study, binary MeVO detection (yes/no) based on mCTA-derived tissue maps had a sensitivity of 90.7% (95%CI: 79.7-96.9%), specificity of 82.2% (95%CI: 70.5-90.8%), a positive predictive value of 81.7% (95%CI: 69.6-90.5), a negative predictive value of 91.1% (95%CI: 80.4-97.0), and an area under the curve (AUC) of 0.87 (95%CI: 0.80-0.93) compared to expert reads of baseline mCTA source images. Interrater agreement was good, with an unweighted Cohen's kappa of 0.72 (95%CI: 0.60-0.85). The overall accuracy of mCTA tissue map based MeVO detection was 86% (100/116). Occlusion location based on mCTA tissue maps was correctly estimated in 70% (81/116) of cases.

Agreement of mCTA and CTP predicted infarct volumes and measured final infarct volume

The mean difference between the mCTA and CTP predicted infarct volumes was 4.8 mL (LoA, –58.5 to 68.1; P=0.56), CCC was 0.66 (95%CI: 0.56 to 0.76; P<0.01) and ICC was 0.68 (95%CI: 0.62 to 0.80; P<0.01).

The mean difference between the mCTA predicted infarct volume and follow-up infarct volume was -16.6 mL (LoA, –64.7 to 31.6; P=0.53), which was less than the CTP predicted infarct volume of -21.4 mL (LoA, –72.5 to 29.8; P=0.54). The CCC between the mCTA

predicted and follow-up infarct volume was 0.57 (95%CI: 0.43 to 0.70; P<0.01), and the ICC was 0.59 (95%CI: 0.48 to 0.72; P<0.01).

Spatial agreement between mCTA and CTP predicted infarct volume and measured final infarct volume

The median DSC between mCTA and CTP predicted infarct volume was 33.5% (IQR: 18.7% to 48.8%) for 58 patients with MeVOs. The median DSCs between mCTA predicted infarct volume and follow up infarct volume and between CTP predicted infarct volume and follow up infarct volume ranged from 23.5% to 37.8%.

6.4 DISCUSSION

EVT for AIS due to MeVOs is seen as the next frontier for the advancement of current stroke treatment paradigms (44). This pilot study shows that mCTA-derived tissue maps also allow for feasible detection of MeVOs in most cases.

Volumetric analyses showed a mean difference in predicted infarct volume of 4.8 ml when comparing mCTA and CTP maps, with a modest CCC of 0.65 and an ICC of 0.67. Because CTP and mCTA employ similar imaging techniques, they can both be used to predict tissue fate on a voxel-by-voxel basis with good agreement. The differences between mCTA-based predicted final infarct volume and "true" (expert contoured) final infarct volumes on follow up was less than that which was predicted using CTP-derived maps, with a modest CCC and ICC of 0.55 and 0.58, respectively. Both CTP and mCTA predicted final infarct volumes were underestimated, regardless of reperfusion status.

The overall spatial agreement between CTP and mCTA predicted infarct volumes was moderate, with a DSC 38.5%. The same was true between mCTA predicted follow-up infarct volume and measured infarct volume (DSC = 23.5%) and CTP predicted follow-up infarct volume and measured infarct volume (DSC = 32.5%). Spatial agreement was worse in the non-reperfused group, probably due to infarct growth, which biases the DSC. Another factor contributing to low spatial agreement could be the co-registration of different imaging modalities.

This study has several limitations. First, the current models were derived using only imaging-based information. Second, accurate measurement of final infarct volume is challenging, with a multitude of factors such as modality, time from onset to imaging and reperfusion, collateral status, tissue tolerance to ischemia, and infarct location likely influencing the results (45). Third, although the mCTA models have now been tested in patients with both LVOs and MeVOs, their applicability needs to be expanded to include more diverse cases (e.g., stroke mimics, small vessel occlusions). Similarly, testing of the models should be performed in external, larger, and more diverse datasets, a necessary step before implementing our results into clinical practice.

6.5 CONCLUSION

mCTA-derived tissue maps can be used to accurately detect MeVO stroke and automatically predict tissue fate with similar accuracy to CTP imaging. Thus, mCTA-derived tissue maps could be used as for patient selection in a randomized MeVO EVT trial as well as in daily clinical practice, particularly in centers in which CTP is not available.

7. Chapter 7 – Results summary

The main aim of this thesis was to investigate and evaluate possible further utilizations of CT imaging modalities in acute stroke care. Several practical implications can be drawn from the finding reported in this thesis.

First, we showed in **Chapter 2** that collateral grading evaluated on the multiphase CTA correlates with increasing perfusion lesion volumes automatically derived from CTP. In the author's opinion these findings support the paradigm that CTP is not necessary in the first 6 hours from the stroke symptom onset while the median volume of the ischemic core remained relatively small even in the patients with poor collaterals. The reported perfusion lesion volumes might be used as an estimate of the probable ischemic core and severely hypoperfused tissue based on the collateral grade on mCTA, which can be easily implemented and thus can be an attractive tool in smaller hospitals and places where CTP is not available.

It was demonstrated in **Chapter 3** that the early ischemic changes can be assessed with higher accuracy on CTP maps (specifically on CBF<30% and Tmax >10s) compared to the expert reading on NCCT. Despite the automatic software analysis of early ischemic changes on NCTT showed the lowest accuracy and sensitivity, its accuracy of 0.76 was comparable with the expert consensus reading and can still be considered as good. In author's opinion, this finding encourages the use of automatic software analysis in clinical practice especially by less experienced readers to fasten the AIS patients triage and prevent any delays in treatment initiation.

Results reported in **Chapter 4** demonstrating the high accuracy of the automatic anterior LVO detection using the machine learning based software tool supports the generalizability of the software's use in routine clinical practice. The findings in this study further encourages the use automatic software tools in acute stroke care to quickly and accurately detecting patients with LVO who may likely require immediate medical attention and benefit from timely treatment.

The novel time-variant mCTA display format was evaluated in **Chapter 5**. We showed that the collateral extent assessment on time-variant mCTA maps improved prediction of good outcome and had similar value in follow-up infarct volume prediction compared to conventional mCTA collateral grading. While the interpretation of collateral status on mCTA requires some degree of experience and suffers from some degree of inter-rater variability, the time-variant mCTA display format represents a suitable alternative to facilitate interpretation of the collateral status.

Another machine learning based application of mCTA was evaluated in **Chapter 6**. mCTA-derived tissue maps as an alternative to CTP maps predicting ischemic core and penumbra. It the presented study, we showed that mCTA-derived tissue maps can be used to accurately detect MeVO stroke which is believed to be the next frontier for EVT. We also demonstrated that tissue fate can be predicted with similar accuracy to CTP maps. The clinical implication of these findings lies in the possibility of using mCTA-derived tissue maps to detect MeVO EVT candidates and estimate the benefit of treatment (volume of potentially salvageable tissue) particularly in centers in which CTP is not available.

8. REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the american heart association. Circulation 2022;145:e153-e639.
2. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. aspects study group. alberta stroke programme early CT score. Lancet (London, England) 2000;355:1670-1674.
3. Naylor J, Churilov L, Rane N, Chen Z, Campbell BCV, Yan B. Reliability and utility of the Alberta Stroke Program Early Computed Tomography score in hyperacute stroke. J Stroke Cerebrovasc Dis 2017;26:2547-2552.
4. Nagel S, Sinha D, Day D, et al. E-aspects software is non-inferior to neuroradiologists in applying the ASPECT score to computed tomography scans of acute ischemic stroke patients. Int J Stroke 2017;12:615-622.
5. Herweh C, Ringleb PA, Rauch G, et al. Performance of e-ASPECTS software in comparison to that of stroke physicians on assessing CT scans of acute ischemic stroke patients. Int J Stroke 2016;11:438-445.
6. Menon BK, D'Esterre CD, Qazi EM, et al. Multiphase CT angiography: A new tool for the imaging triage of patients with acute ischemic stroke. Radiology 2015;275:510-520.
7. Demeestere J, Wouters A, Christensen S, Lemmens R, Lansberg MG. Review of perfusion imaging in acute ischemic stroke: From time to tissue. Stroke 2020;51:1017-1024.
8. Olivot JM, Mlynash M, Inoue M, et al. Hypoperfusion intensity ratio predicts infarct progression and functional outcome in the DEFUSE 2 cohort. Stroke 2014;45:1018-1023.
9. Ospel JM, Volny O, Qiu W, et al. Displaying multiphase CT angiography using a time-variant color map: Practical considerations and potential applications in patients with acute stroke. AJNR Am J Neuroradiol 2020;41:200-205.
10. Qiu W, Kuang H, Ospel JM, et al. Automated prediction of ischemic brain tissue fate from multiphase computed tomographic angiography in patients with acute ischemic stroke using machine learning. J Stroke 2021;23:234-243.
11. Menon BK, Qazi E, Nambiar V, et al. Differential effect of baseline computed tomographic angiography collaterals on clinical outcome in patients enrolled in the Interventional Management of Stroke III trial. Stroke 2015;46:1239-1244.
12. Berkhemer OA, Jansen IGH, Beumer D, et al. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. Stroke 2016;47:768-776.
13. Bang OY, Saver JL, Buck BH, et al. Impact of collateral flow on tissue fate in acute ischaemic stroke. 79:625-629.
14. De Havenon A, Mlynash M, Kim-Tenser MA, et al. Results from DEFUSE 3: Good collaterals are associated with reduced ischemic core growth but not neurologic outcome. Stroke 2019;50:632-638.
15. Lin L, Yang J, Chen C, et al. Association of collateral status and ischemic core growth in patients with acute ischemic stroke. Neurology 2021;96:e161-e170.

16. Bang OY, Saver JL, Kim SJ, et al. Collateral flow averts hemorrhagic transformation after endovascular therapy for acute ischemic stroke. Stroke 2011;42:2235-2239.
17. Potreck A, Scheidecker E, Weyland CS, et al. RAPID CT perfusion-based relative CBF identifies good collateral status better than hypoperfusion intensity ratio, CBV-index, and Time-to-maximum in anterior circulation stroke. AJNR Am J Neuroradiol June 2022. doi:10.3174/ajnr.A7542
18. Lyndon D, van den Broek M, Niu B, Yip S, Rohr A, Settecase F. Hypoperfusion intensity ratio correlates with CTA collateral status in large-vessel occlusion acute ischemic stroke. Am J Neuroradiol 2021;42:1380-1386.
19. Guenego A, Fahed R, Albers GW, et al. Hypoperfusion intensity ratio correlates with angiographic collaterals in acute ischaemic stroke with M1 occlusion. Eur J Neurol 2020;27:864-870.
20. Mokin M, Levy EI, Saver JL, et al. Predictive value of rapid assessed perfusion thresholds on final infarct volume in SWIFT PRIME (Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment). Stroke 2017;48:932-938.
21. Inoue M, Mlynash M, Straka M, et al. Patients with the malignant profile within 3 hours of symptom onset have very poor outcomes after intravenous tissue-type plasminogen activator therapy. Stroke 2012;43:2494-2496.
22. Albers GW, Goyal M, Jahan R, et al. Ischemic core and hypoperfusion volumes predict infarct size in SWIFT PRIME.
23. Padroni M, Bernardoni A, Tamborino C, et al. Cerebral blood volume ASPECTS is the best predictor of clinical outcome in acute ischemic stroke: A retrospective, combined semi-quantitative and quantitative assessment. Chang AYW, ed. PLoS One 2016;11:e0147910.
24. Aviv RI, Mandelcorn J, Chakraborty S, et al. Alberta Stroke Program Early CT scoring of CT perfusion in early stroke visualization and assessment. AJNR Am J Neuroradiol 2007;28:1975-1980.
25. Sillanpaa N, Saarinen JT, Rusanen H, et al. CT perfusion aspects in the evaluation of acute ischemic stroke: thrombolytic therapy perspective. Cerebrovasc Dis Extra 2011;1:6-16.
26. Sundaram VK, Goldstein J, Wheelwright D, et al. Automated ASPECTS in acute ischemic stroke: A comparative analysis with CT perfusion. AJNR Am J Neuroradiol 2019;40:2033-2038.
27. Duloquin G, Graber M, Garnier L, et al. Incidence of acute ischemic stroke with visible arterial occlusion. Stroke 2020;51:2122-2130.
28. Malhotra K, Gornbein J, Saver JL. Ischemic strokes due to large-vessel occlusions contribute disproportionately to stroke-related dependence and death: A review. Front Neurol 2017;8.
29. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the american heart association/american stroke association. Stroke 2019;50:E344-E418.
30. Demchuk AM, Menon BK, Goyal M. Comparing vessel imaging: Noncontrast computed tomography/computed tomographic angiography should be the new minimum

standard in acute disabling stroke. Stroke 2016;47:273-281.
31. Menon BK. Neuroimaging in acute stroke. Contin Lifelong Learn Neurol 2020;26:287-309.
32. Saver JL. Time is brain—quantified. Stroke 2006;37:263-266.
33. Hill MD, Goyal M, Menon BK, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): A multicentre, double-blind, randomised controlled trial. Lancet 2020;395:878-887.
34. Ginsberg MD, Palesch YY, Hill MD, et al. High-dose albumin treatment for acute ischaemic stroke (ALIAS) part 2: A randomised, double-blind, phase 3, placebo-controlled trial. Lancet Neurol 2013;12:1049-1058.
35. Coutts SB, Dubuc V, Mandzia J, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. Stroke 2015;46:769-774.
36. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): A prospective observational study. Lancet Neurol 2012;11:307-314.
37. Amukotuwa SA, Straka M, Smith H, et al. Automated detection of intracranial large vessel occlusions on computed tomography angiography a single center experience. Stroke 2019;50:2790-2798.
38. Hassan AE, Ringheanu VM, Rabah RR, Preston L, Tekle WG, Qureshi AI. Early experience utilizing artificial intelligence shows significant reduction in transfer times and length of stay in a hub and spoke model. Interv Neuroradiol 2020;26:615-622.
39. Saver JL, Chapot R, Agid R, et al. Thrombectomy for distal, medium vessel occlusions: A consensus statement on present knowledge and promising directions. Stroke 2020:2872-2884.
40. Fasen BACM, Heijboer RJJ, Hulsmans FJH, Kwee RM. CT angiography in evaluating large-vessel occlusion in acute anterior circulation ischemic stroke: Factors associated with diagnostic error in clinical practice. Am J Neuroradiol 2020;41:607-611.
41. Qiu W, Kuang H, Ospel JM, et al. Automated prediction of ischemic brain tissue fate from multiphase computed tomographic angiography in patients with acute ischemic stroke using machine learning. J stroke 2021;23:234-243.
42. Najm M, Kuang H, Federico A, et al. Automated brain extraction from head CT and CTA images using convex optimization with shape propagation. Comput Methods Programs Biomed 2019;176:1-8.
43. D'Esterre CD, Boesen ME, Ahn SH, et al. Time-dependent computed tomographic perfusion thresholds for patients with acute ischemic stroke. Stroke 2015;46:3390-3397.
44. Goyal M, Ospel JM, Menon BK, Hill MD. MeVO: the next frontier? J Neurointerv Surg 2020;12:545-547.
45. Goyal M, Ospel JM, Menon B, et al. Challenging the ischemic core concept in acute ischemic stroke imaging. Stroke 2020:3147-3155.

9. OVERVIEW OF AUTHOR'S PUBLICATIONS

Original scientific papers published in an impacted journal

Cimflova P., Holikova K., Kim B.J., et al. Correlation of the multiphase CTA collateral score and the automatically-derived CT perfusion volumes. – *submitted to Journal of Neuorimaging*

Kashani N, Cimflova P, Ospel JM, Kappelhof M, Singh N, McDonough R V., et al. Desired Qualities of Endovascular Tools and Barriers to Treating Medium Vessel Occlusion MeVO. *Clin Neuroradiol* 2022. July 2022:1-6 – IF 3.649

Cimflova P, Golan R, Ospel JM, Sojoudi A, Duszynski C, Elebute I, et al. Validation of a machine learning software tool for automated large vessel occlusion detection in patients with suspected acute stroke. *Neuroradiology.* May 2022:1-11. – IF 2.995

Cimflova P, Ospel JM, Marko M, Menon BK, Qiu W. Variability assessment of manual segmentations of ischemic lesion volume on 24-h non-contrast CT. *Neuroradiology*. 2022;64(6):1165-1173. – IF 2.995

McDonough R V., Qiu W, Ospel JM, Menon BK, Cimflova P, Goyal M. Multiphase CTA-derived tissue maps aid in detection of medium vessel occlusions. *Neuroradiology*. 2022;64(5):887-896. – IF 2.995

El-Hariri H, Souto Maior Neto LA, Cimflova P, Bala F, Golan R, Sojoudi A, et al. Evaluating nnU-Net for early ischemic change segmentation on non-contrast computed tomography in patients with Acute Ischemic Stroke. *Comput Biol Med*. 2022;141. doi: 10.1016/j.compbiomed.2021.105033 – IF 7.469

Kappelhof M, Ospel J, Kashani N, Cimflova P, Singh N, Almekhlafi MA et al. Influence of intravenous alteplase on endovascular treatment decision-making in acute ischemic stroke due to primary medium-vessel occlusion: A case-based survey study. *J Neurointerv Surg*. 2022;14(5):439-443. – IF 8.572

Cimflova P, Kappelhof M, Singh N, Kashani N, Ospel JM, McDonough R, et al. Factors influencing thrombectomy decision making for primary medium vessel occlusion stroke. *J Neurointerv Surg*. 2022;14(4):350-355. – IF 8.572

Marko M, Cimflova P, Poppe AY, Kashani N, Singh N, Ospel J, et al. Management and outcome of patients with acute ischemic stroke and tandem carotid occlusion in the ESCAPE-NA1 trial. *J Neurointerv Surg*. 2022;14(5):429-433. – IF 8.572

Cimflova P, Singh N, Ospel JM, Marko M, Kashani N, Mayank A, et al. Association of Stent-Retriever Characteristics in Establishing Successful Reperfusion During Mechanical Thrombectomy: Results from the ESCAPE-NA1 Trial. *Clin Neuroradiol.* January 2022. doi: 10.1007/s00062-021-01123-0 – IF 3.649

Kashani N, Cimflova P, Ospel JM, Singh N, Almekhlafi MA, Rempel J, et al. Endovascular Device Choice and Tools for Recanalization of Medium Vessel Occlusions: Insights From the MeVO FRONTIERS International Survey. *Front Neurol.* 2021;12. doi: 10.3389/fneur.2021.735899 – IF 4.086

Ospel JM, Hill MD, Demchuk A, Menon BK, Thornton J,… Cimflova P, et al. Clinical impact of EVT with failed reperfusion in patients with acute ischemic stroke: results from the ESCAPE and ESCAPE-NA1 trials. *Neuroradiology.* 2021;63(11):1883-1889. – IF 2.995

Cimflova P, McDonough R, Kappelhof M, Singh N, Kashani N, Ospel J, et al. Perceived Limits of Endovascular Treatment for Secondary Medium-Vessel-Occlusion. Stroke. *Am J*

Neuroradiol. 2021;42(12):2188-2193. – IF 3.825

Cimflova P, Ospel J, Marko M, Menon B, Qiu W. Variability assessment of manual segmentations of ischemic lesion volume on 24-h non-contrast CT. *Neuroradiol 2021*. 2021;1:1-9. – IF 2.995

Cimflova P, Kral J, Volny O, Horn M, Ojha P, Cabal M, et al. MRI Diffusion-Weighted Imaging to Measure Infarct Volume: Assessment of Manual Segmentation Variability. *J Neuroimaging*. 2021;31(3):541-550. – IF 2.324

Cimflova P, Özlük E, Korkmazer B, Ahmadov R, Akpek E, et al. Long-term safety and efficacy of distal aneurysm treatment with flow diversion in the M2 segment of the middle cerebral artery and beyond. *J Neurointerv Surg*. 2021;13(7):631-636. – IF 5.836

Ospel JM, Cimflova P, Volny O, Qiu W, Hafeez M, et al. Utility of Time-Variant Multiphase CTA Color Maps in Outcome Prediction for Acute Ischemic Stroke Due to Anterior Circulation Large Vessel Occlusion. *Clin Neuroradiol*. 2021;31(3):783-790. – IF 3.649

Ospel JM, Cimflova P, Marko M, Mayank A, Hafeez M, Almekhlafi MA, et al. Prevalence and Outcomes of Medium Vessel Occlusions With Discrepant Infarct Patterns. *Stroke*. 2020;51(9):2817-2824. – IF 7.914

Volny O, Zerna C, Tomek A, Bar M, Rocek M, Padr R, … Cimflova P, et al. Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. *Neurology*. 2020;95(24):e3364-e3372. – IF 9.901

Ospel JM, Kashani N, Mayank A, Cimflova P, Heran M, Pandey S, et al. Impact and prevention of errors in endovascular treatment of unruptured intracranial aneurysms. *Interv Neuroradiol*. 2020;26(5):575-581. – IF 1.610

Cimflova P, Volny O, Mikulik PR, Tyshchenko B, Belaskova S, Vinklarek J, et al. Detection of ischemic changes on baseline multimodal computed tomography: expert reading vs. Brainomix and RAPID software. *J Stroke Cerebrovasc Dis*. 2020;29(9):104978. – IF 9.901

Vanicek J, Cimflova P, Bulik M, Jarkovsky J, Prelecova V, Szeder V, et al. Single-Centre Experience with Patients Selection for Mechanical Thrombectomy Based on Automated Computed Tomography Perfusion Analysis–A Comparison with Computed TomographyCT Perfusion Thrombectomy Trials. *J Stroke Cerebrovasc Dis*. 2019;28(4):1085-1092. – IF 9.901

Volny O, Krajina A, Belaskova S, Bar M, Cimflova P, Herzig R, et al. Mechanical thrombectomy performs similarly in real world practice: A 2016 nationwide study from the Czech Republic. *J Neurointerv Surg*. 2018;10(8):741-745. – IF 1.646

Volny O, Justanova M, Cimflova P, Kasickova L, Svobodova I, Muzik J, et al. 24-Hour Alberta Stroke Program Early CT Score Assessment in Post-Stroke Spasticity Development in Patients with a First Documented Anterior Circulation Ischemic Stroke. *J Stroke Cerebrovasc Dis*. 2018;27(1):240-245. – IF 1.646

Volny O, Cimflova P, Lee TY, et al. Permeability surface area product analysis in malignant brain edema prediction – A pilot study. *J Neurol Sci*. 2017;376:206-210. – IF 2.448

Volny O, Cimflova P, Szeder V. Inter-Rater Reliability for Thrombolysis in Cerebral Infarction with TICI 2c Category. *J Stroke Cerebrovasc Dis*. 2017;26(5):992-994. – IF 1.598

Volny O, Cimflova P, Kadlecova P, Vanek P, Vanicek J, et al. Single-Phase Versus Multiphase CT Angiography in Middle Cerebral Artery Clot Detection—Benefits for Less Experienced Radiologists and Neurologists. *J Stroke Cerebrovasc Dis*. 2017;26(1):19-24. – IF 1.598

Volny O, Bar M, Krajina A, Cimflova P, Kasickova L, et al. A Comprehensive Nationwide

Evaluation of Stroke Centres in the Czech Republic Performing Mechanical Thrombectomy in Acute Stroke in 2016. *Cesk Slov Neurol N* 2017;80/113(4):445-450. – IF 0.33

Volny O, Cimflova P, Mikulik R. Ipsilateral Sinus Hypoplasia and Poor Leptomeningeal Collaterals as Midline Shift Predictors. *J Stroke Cerebrovasc Dis*. 2016;25(7):1792-1796. – IF 1.517

Volný O, Cimflová P, D'Esterre CD. Využití CT perfuze a multifázické CT angiografie v predikci rozvoje maligního mozkového edému u pacientů s akutním mozkovým infarktem. *Ces a Slov Neurol a Neurochir*. 2016;79(2):213-217. – IF 0.33

Other papers published in an impacted journal (overview, methodology, case report)

Goyal M, Cimflova P, Ospel J, Chapot R. Endovascular treatment of anterior cerebral artery occlusions. *J Neurointerv Surg*. 2021. doi: 10.1136/neurintsurg-2021-017735

Ryska P, Lojik M, Kocer N, Zelenak K, Cesak T, Cimflova P, et al. Mechanical thrombectomy performed in thrombosed fusiform aneurysm after surgery for craniopharyngioma in adult. Biomed Pap. 2021;165(3):336-341.

Vališ K, Cimflová P, Vaníček J, Volný O. Acute therapy of ischemic stroke - news in mechanical trombectomy. Neurol pro praxi. 2020;21(3):191-196.

Goyal M, Sutherland GR, Lama S, Cimflova P, Kashani N, Mayank A, et al. Neurointerventional Robotics: Challenges and Opportunities. Clin Neuroradiol. 2020;30(2):203-208.

Cimflová P, Vališ K, Volný O, Vinklárek J, Haršány M, Mikulík R. Diagnostika ischemických CMP - přehled zobrazovacích metod a jejich využití v praxi. Česká Radiol. 2019;73(3):150-159.

Vinklárek J, Haršány M, Cimflová P, Mikulík R, Volný O. Computed tomography in acute ischemic stroke. Neurol pro praxi. 2018;19(4):256-261.

Volný O, Kašičková L, Coufalová D, Cimflová P, Novák J. MikroRNA u cerebrovaskulárních onemocnění-od patofyziologie k potenciálnim bionriarkerům. Ces a Slov Neurol a Neurochir. 2016;79(3):287-293.

Volný O, Kašičková L, Coufalová D, Cimflová P, Novák J. microRNAs in Cerebrovascular Disease. Adv Exp Med Biol. 2015;888:155-195.

Pažourková M, Svátková A, Kočvarová J, Chrastina J, Cimflová P. Význam magnetické rezonance v diagnostice epilepsie. Ces a Slov Neurol a Neurochir. 2015;78(4):394-400.

Chapters in textbooks

Ospel JM, Cimflova P, Goyal M. Stroke Imaging. Atlas Emerg Imaging from Head-to-Toe. 2021:1-14.

Volny O, Kasickova L, Coufalova D, Cimflova P, Novak J. MicroRNA in Cerebrovascular Diseases. In: Santulli G. (Ed.) microRNA: Basic Science. From Molecular Biology to Clinical Practice. 1st ed. Switzerland: Springer International Publishing 2015.

Lectures and poster presentations at conferences and meetings

a) posters and e-posters presentation

Cimflova P., Holikova K., Kim B.J., et al. Correlation of the automatically-derived CT perfusion volumes and the multiphase CTA collateral score. *8th European Stroke Organisation Conference, May 2022, Lyon, Francie*

Cimflova P., Golan R., Bala F., et al. Validation of a machine learning-driven algorithm for large vessel occlusion detection in acute ischemic stroke. *7th European Stroke Organisation Conference - virtual, September 2021*

Cimflova P., El-Hariri H., Neto L.M., et al. Automated Alberta Stroke Program Early CT Score assessment using a machine learning based algorithm. *7th European Stroke Organisation Conference – virtual, September 2021*

Cimflova P., McDonough R., Kappelhof M., et al. Perceived Limits of Endovascular Treatment for Secondary Medium Vessel Occlusion Stroke. *SNIS 2021 - virtual, July 2021*

Cimflova P., Kappelhof M., Singh N.,et al. Factors Influencing Thrombectomy decision-Making for Primary Medium Vessel Occlusion Stroke (MeVO). *SNIS 2021 – virtual, July 2021*

Cimflova P., Kappelhof M., Ospel J. et. al. Medium Vessel Occlusions – the Next Frontier in Endovascular Treatment for Acute Ischemic Stroke. *ASNR 59th Annual Meeting – virtual, May 2021 (awarded MAGNA CUM LAUDE)*

Cimflova P., Singh N., Ospel, J. et al., on behalf of ESCAPE-NA1 investigators. Quality of Reperfusion – Association of stent-retriever characteristics and successful reperfusion in ESCAPE NA1 dataset. *International Stroke Conference 2021 – virtual, February 2021*

Cimflova P., Singh N., Ospel, J. et al., on behalf of ESCAPE-NA1 investigators. Quality of Reperfusion and Clinical Outcome in ESCAPE NA1 trial. *International Stroke Conference 2021 – virtual, February 2021*

Cimflova P., Volny O., Vanicek J., Belaskova S. Can Early Ischemic Changes Be Detected on CT modalities with Comparable Reliability? - a comparison of e-ASPECTS, expert rating and CT Perfusion Maps. *10th ESMINT Congress, September 2018, Nice, Francie*

Cimflova P., Volny O., Szeder V., Sayre J.W., Vanicek J., Savor J. TICI, HICI, AICI – is there a better score for perfusion assessment? *3rd European Stroke Organisation Conference, May 2017, Prague, Czech republic.*

Cimflova P., Volny O., Kadlecova P., Mikulik R., Menon B.K. Single-phase versus multiphase CTA in clot/s detection in middle cerebral artery – comparison of both methods. *2nd European Stroke Organisation Conference, May 2016, Barcelona, Spain.*

Cimflova P., Vanicek J. Kazuistika: Fatální cervikální poranění s postižením tepen vertebrobazilárního povodí. *5th Congress of traumatology and musculoskeletal radiology*, *April 2017, Brno*

b) oral presentations and lectures

„Distal clot, treat or not“, EXMINT 4.2 / EXMINT 3.2 (European Stroke Course in Minimally Invasive Neurological Therapy), Prague, March 2022/2021

„Advanced Imaging in the 0-6 hour time window“, European Course in Interventional Neuroradiology, 2nd Cycle, Module 1, December 2021

„MRI in acute stroke“, „What did the trials show us“, EXMINT 4.1 / EXMINT 3.1 / EXMINT 2.1 European Stroke Course in Minimally Invasive Neurological Therapy), Prague, November 2019/2020/2021

„Stroke Imaging – CT is enough!“, Stroke Winter School, Bern – virtual, January 2021

„Přínos perfusních metod a automatického software u akutní iCMP“, VIII. Český neuroradiologický kongres, October 2019

XXIV. Pracovní sympozium CSIR, Špindlerův Mlýn, June 2019

„Non enhanced CT and CTA in acute stroke“, „Perfusion imaging technique and background“, „MRI in acute stroke“, EXMINT 1.1 (European Stroke Course in Minimally Invasive Neurological Therapy), Prague, November 2018

„CT/CTA zobrazování při diagnostice CMP“, 46. Český a slovenský cerebrovaskulární kongres, Mikulov, September 2018

XXIII. Pracovní sympozium CSIR, Harrachov, June 2018

„Zobrazezní u CMP po 6 hodin od vzniku“, V. Stoke Workshop, Konopiště, April 2018

„Praktické základy pro hodnocení nativního CT“, „Praktické základy pro hodnocení CT angiografie“, „Základy fyzikálních principů CT (MR) perfúze“**,** hands-on course Neurozobrazování u cévní mozkové příhody, Brno, January 2018 - main organizer and lecturer of 3 days hands-on course focused on stroke imaging

„Zobrazení kolaterál“, IV. Stroke Workshop, Konopiště, April 2017

„Zobrazení u CMP během prvních 6 hodin“, III. Stroke Workshop, Konopiště, April 2016

„Ruptured tip basilar aneurysm“, MENCC 2015 (Middle-east European Neurointerventional Club Course), Hradec Králové, November 2015

„Ruptured tip basilar aneurysm – It’s not just about coiling“, 7th ESMINT Congress, Nice, France, September 2015

„CT Perfusion and Multiphase CT Angiography in Malignant Brain Edema Prediction in Patients with Acute Ischemic Stroke“, XXII. Conference of Young Physicians, Brno, soutěžní přednáška (1. místo), May 2015

„CT perfusní zobrazení“, Philips Workshop, Dolní Morava, duben 2015