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Die Rolle der multiparametrischen Computertomographie zur Prädiktion des morphologischen und funktionellen Outcomes nach akutem ischämischem Schlaganfall

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

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München, 30.01.2022	Felix Schuler
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Inhaltsverzeichnis

1 Abkürzungsverzeichnis

AHA	*American Heart Associaton*
ASA	*American Stroke Association*
ASPECTS	*Alberta Stroke Program Early CT Score*
ATP	Adenosintriphosphat
CBF	Zerebraler Bluttfluss *(cerebral blood flow)*
CBV	Zerebrales Blutvolumen *(cerebral blood volume)*
CCD	Gekreuzt zerebelläre Diaschisis *(crossed cerebellar diaschisis)*
CT	Computertomographie *(computed tomography)*
CTA	Computertomographie-Angiographie *(computed tomography angiography)*
CTP	Computertomographie-Perfusion *(computed tomography perfusion)*
CVR	Zerebraler Gefäßwiderstand *(cerebrovascular resistance)*
DWI	Diffusionswichtung *(diffusion weighted imaging)*
EVT	Endovaskuläre Thrombektomie *(endovascular thombectomy)*
HU	Hounsfield-Einheiten *(Hounsfield-Units)*
ICP	Intrazerebraler Druck *(intracerebral pressure)*
IVT	Intravenöse Thrombolyse *(intravenous thrombolysis)*
MAP	Arterieller Mitteldruck *(mean arterial pressure)*
MRT	Magnetresonanztomographie
MTT	Mittlere Passagezeit *(mean transit time)*
NCCT	Native Computertomographie *(non contrast computed tomography)*
rtPA	Alteplase *(recombinant tissue plasminogen activator)*
TAC	Schwächungs-Zeitkurve *(time attenuation curve)*
TIA	Transient ischämische Attacke
TOAST	*Trial of Org 10172 in Acute Stroke Treatment*
TTD	*Time to drain*
TTP	*Time to peak*
WHO	*World Health Organisation*

2 Publikationsliste

Während meiner Doktorandentätigkeit in der Klinik und Poliklinik für Radiologie der Ludwig-Maximilians-Universität München unter Betreuung von Professor Dr. Kolja Thierfelder und PD Dr. Wolfgang Kunz sind folgende wissenschaftliche Arbeiten unter meiner Mitwirkung entstanden:

Wavelet-Based Angiographic Reconstruction of Computed Tomography Perfusion Data: Diagnostic Value in Cerebral Venous Sinus Thrombosis

Kunz, Wolfgang G.; **Schuler, Felix;** Sommer, Wieland H.; Fabritius, Matthias P.; Havla, Lukas; Meinel, Felix; Reiser, Maximilian F.; Ertl-Wagner, Birgit; Thierfelder, Kolja M.

INVESTIGATIVE RADIOLOGY
DOI: 10.1097/RLI.0000000000000337
Published: MAY 2017
Impact factor 2017: 6,224

Crossed cerebellar diaschisis in acute ischemic stroke: Impact on morphologic and functional outcome

Kunz, Wolfgang G.; Sommer, Wieland H.; Hoehne, Christopher; Fabritius, Matthias P.; **Schuler, Felix**; Dorn, Franziska; Othman, Ahmed E.; Meinel, Felix G.; von Baumgarten, Louisa; Reiser, Maximilian F.; Ertl-Wagner, Birgit; Thierfelder, Kolja M.

JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM
DOI: 10.1177/0271678X16686594
Published: NOVEMBER 2017
Impact factor 2017: 6,045

Differential Benefit of Collaterals for Stroke Patients Treated with Thrombolysis or Supportive Care: A Propensity Score Matched Analysis

Schuler, Felix; Rotkopf, Lukas T.; Apel, Daniel; Fabritius, Matthias P.; Tiedt, Steffen; Wollenweber, Frank A.; Kellert, Lars; Dorn, Franziska; Liebig, Thomas; Thierfelder, Kolja M.; Kunz, Wolfgang G.

CLINICAL NEURORADIOLOGY
DOI: 10.1007/s00062-019-00815-y
Published: AUGUST 2019
Impact factor 2019: 3,183

Die beiden letztgenannten Publikationen sind Bestandteil dieser kumulativen Dissertation.

3 Eigenanteil der Originalarbeiten

Das Manuskript „*Crossed cerebellar diaschisis in acute ischemic stroke: Impact on morphologic and functional outcome*" wurde 2017 im *Journal of Cerebral Blood Flow and Metabolism* mit einem Impact factor von 6,045 publiziert.

Im Rahmen dieser Studie habe ich maßgeblich an der Datenerhebung und -analyse sowie der Verfassung und Gestaltung des Manuskriptes mitgewirkt.

Das Manuskript „*Differential Benefit of Collaterals for Stroke Patients Treated with Thrombolysis or Supportive Care: A Propensity Score Matched Analysis*" wurde 2019 in der Fachzeitschrift *Clinical Neuroradiology* mit einem Impact factor von 3,183 veröffentlicht.

Für diese Publikation habe ich das Studiendesign konzipiert und war für die Durchführung zuständig. Weiterhin habe ich die statistischen Analysen ausgeführt sowie das Manuskript entworfen und verfasst.

4 Einleitung

4.1 Epidemiologie des Schlaganfalls

Der Schlaganfall ist für eine massive sozioökonomische Belastung der heutigen Gesellschaft verantwortlich.[1, 2] Er ist gemäß Daten der *World Health Organisation* (WHO) weltweit die zweithäufigste Todesursache[3] und stellt zudem den häufigsten Grund für eine erworbene Behinderung im Erwachsenenalter dar.[4, 5]

Etwa alle vier Minuten erleidet ein Mensch in den USA einen Schlaganfall.[1] In Deutschland sind etwa 250.000 Menschen jährlich von einem Schlaganfall betroffen.[6] Während die Mortalität des ischämischen Schlaganfalls rückläufig ist, ist die Gesamtzahl der Patienten, die einen Schlaganfall erleiden, insgesamt angestiegen.[1]

4.2 Ätiologie des Schlaganfalls

Ein Schlaganfall kann sowohl durch eine Blutung (Hämorrhagie) als auch durch eine Durchblutungsstörung (Ischämie) bedingt sein. Gemäß aktuellen Leitlinien wird der ischämische Schlaganfall als „akutes fokales neurologisches Defizit aufgrund einer umschriebenen Durchblutungsstörung des Gehirns“ definiert.[7, 8] Dieser ist für etwa 87% aller Schlaganfälle verantwortlich. Die restlichen 13% entstehen aufgrund einer Hirnblutung und werden als hämorrhagische Schlaganfälle bezeichnet. Diese entfallen in etwa 10% der Fälle auf intrazerebrale und in etwa 3% auf subarachnoidale Blutungen.[1, 8-10]

Thema dieser Dissertation ist der ischämische Schlaganfall. Diesem können wiederum verschiedene Pathologien zugrunde liegen. In der Klinik und Forschung hat sich diesbezüglich die Klassifikation nach dem *Trial of Org 10172 in Acute Stroke Treatment* (TOAST-Klassifikation) zur Einteilung etabliert.[11] Sie unterteilt den ischämischen Schlaganfall hinsichtlich seiner Ätiologie in fünf Gruppen:

Ischämischer Schlaganfall
Makroangiopathie (*large artery atherosclerosis*)
Kardioembolie *(cardioembolism)*
Mikroangiopathie *(small vessel occlusion)*
Andere bekannte Ursache (z.B. Vaskulitis, Dissektion, Gerinnungsstörung)
Unklare Ätiologie

Tabelle 1 Klassifikation des ischämischen Schlaganfalls nach dem Trial of Org 10172 in Acute Stroke Treatment (TOAST-Klassifikation)[11]

4.3 Pathophysiologie des ischämischen Schlaganfalls

Das Hirngewebe ist sehr empfindlich gegenüber Ischämien. Es besitzt keine eigenen Energiereserven und ist für seinen Metabolismus fast ausschließlich auf Glucose angewiesen. Unter physiologischen Umständen erhält das Gehirn circa 20% des Herzminutenvolumens.[12]

Um eine ausreichende Versorgung des Gehirns sicherzustellen, unterliegt der zerebrale Blutfluss (*cerebral blood flow,* CBF) einer physiologischen Autoregulation. Der CBF ist dabei direkt vom arteriellen Mitteldruck (*mean arterial pressure,* MAP), dem intrazerebralen Druck (*intracerebral pressure,* ICP) sowie dem zerebralen Gefäßwiderstand (*cerebrovascular resistance,* CVR) abhängig.[13]

Es gilt: *CBF = (MAP – ICP) / CVR.*

Durch einen Gefäßverschluss oder eine Gefäßstenose kommt es beim ischämischen Schlaganfall zu einer Störung dieser Autoregulation. Trotz Gegenregulation kann ein ausreichender zerebraler Blutfluss nicht aufrechterhalten werden. Infolgedessen kommt es zu einer fokalen Ischämie des nachgeschalteten Gehirnareals und somit zu einer Minderversorgung an Sauerstoff und Glukose.[14]

Die Ischämie löst eine Kaskade an zellulären Veränderungen aus, welche letztendlich zum Infarkt führen.[14-16] Aufgrund des Sauerstoffmangels kommt es zur anaeroben Glykolyse mit nachfolgendem Mangel an Adenosintriphosphat (ATP)[17] und Laktatazidose sowie zur Störung der elektrischen Aktivität mit Elektrolytverschiebungen von Natrium, Kalium und Kalzium und konsekutivem Ödem.[18, 19] Ferner sind die Freisetzung exzitatorischer Neutrotransmitter (Exzitotoxizität)[20] und die Bildung von freien Radikalen Folgen dieses Mangelzustands.[21, 22]

Diese Prozesse führen über direkte und indirekte Mechanismen zum Zelltod durch Nekrose mit nachfolgender Inflammation. Bei weniger ausgeprägtem Substratmangel kommt es zum programmierten Zelltod durch Apoptose.[23, 24]

Im Zentrum des Infarktes ist der Blutfluss so stark reduziert, dass es zur irreversiblen Schädigung der Zellen kommt, weitestgehend durch Nekrose bedingt. Man spricht vom Infarktkern.[25]

Der Infarktkern wird wiederum von einem Areal mit reduziertem Blutfluss umgeben, welches über leptomeningeale Kollateralen noch teilweise mit Sauerstoff und Glukose versorgt wird. Dieses Areal wird als Penumbra (lat. für Halbschatten) bezeichnet[19] und befindet sich oberhalb der Infarktschwelle. Das bedeutet, dass sich hier Neurone mit bereits gestörter elektrischer Aktivität, jedoch noch teilweise erhaltenem Metabolismus finden.[19, 26, 27] Dauert die Ischämie länger an, kann der Metabolismus nicht mehr

aufrechterhalten werden und es kommt zum Zelluntergang. Bei den Neuronen innerhalb der Penumbra handelt es sich daher um eine Region mit gefährdetem Gewebe, welche bei länger andauernder Ischämie in den wachsenden Infarktkern fallen kann. Hier kann eine rechtzeitige Therapie die Ausdehnung des Infarktkerns und einen weiteren Verlust an funktionsfähigem Gewebe verhindern. Die Penumbra wird daher auch als *tissue at risk* oder *salvageable tissue* bezeichnet.[28]

4.4 Therapie des ischämischen Schlaganfalls

Die Grundlage der Therapie des akuten ischämischen Schlaganfalls besteht in der schnellstmöglichen Reperfusion, also der Wiederherstellung des Blutflusses der ischämischen Region. Da sich der Infarktkern bei länger andauernder Ischämie ausdehnen kann, gilt der Grundsatz *time is brain*, also Zeit ist Hirn.[29]

Kann die Perfusion rechtzeitig wiederhergestellt werden, lässt sich dadurch das *tissue at risk* retten und der Infarktkern kann möglichst klein gehalten werden. Infolgedessen ist mit einer geringeren neurologischen Beeinträchtigung zu rechnen.[25, 30] Durch eine adäquate Therapie lässt sich die Mortalität und schlaganfallbedingte Behinderung zum Teil erheblich vermindern.[31-33]

Grundsätzlich stehen zur kausalen Therapie des ischämischen Schlaganfalls die intravenöse Thrombolyse (*intravenous thrombolysis*, IVT) sowie die endovaskuläre Thrombektomie (*endovascular thrombectomy*, EVT) zur Verfügung.

Den Grundpfeiler der Schlaganfalltherapie stellt die IVT mit der intravenösen Applikation thrombolytischer Substanzen (z.B. Alteplase [=*recombinant tissue plasminogen activator,* rt-PA]) dar. Hierdurch wird das körpereigene Enzym Plasmin aktiviert, was zur Auflösung des Thrombus führt.[34]

Jeder Patient mit alltagsrelevantem neurologischem Defizit ohne Kontraindikationen für eine Lysetherapie sollte in der Akutsituation schnellstmöglich eine IVT erhalten.[35-44] In einer Metaanalyse konnte der positive Einfluss der Thrombolyse auf das Outcome unabhängig von Patientenalter oder dem Schweregrad des Schlaganfalls gezeigt werden.[42]

Da die Wirkung der IVT zeitabhängig ist, ist die Chance auf ein gutes Outcome umso größer, je schneller eine IVT durchgeführt wird.[39-42]

Die Hauptkomplikation besteht in einem gehäuften Auftreten einer hämorrhagischen Transformation bei Patienten, welche eine Lysetherapie erhalten. Diese trat umso wahrscheinlicher auf, je später die IVT durchgeführt wurde.[9, 35, 39, 41, 44]

Die *ECASS II* Studie[38] unterteilt die hämorrhagische Transformation in drei weitere Gruppen. Die hämorrhagische Infarzierung (*hemorrhagic infarction,* HI) bezeichnet petechiale Einblutungen im Infarktbereich, das Parenchymhämatom (*parenchymal hematoma,* PH) flächige Einblutungen mit zunehmend raumfordernder Wirkung und die symptomatische intrakranielle Blutung (*symptomatic intracranial hemorrhage,* sICH) jegliche Blutung bei klinischer Verschlechterung des Patienten. Einen Einfluss auf das Outcome bei Schlaganfallpatienten konnte beim PH und der sICH nachgewiesen werden.[45, 46]

In aktuellen Leitlinien ist eine Lysetherapie daher bis zu viereinhalb Stunden nach Symptombeginn empfohlen.[7] Innerhalb dieses relativ kurzen Zeitfensters erhalten jedoch weniger als 10% aller Schlaganfallpatienten eine intravenöse Thrombolyse.[47] Über diesen Zeitraum hinaus ist derzeit unklar, ob der Nutzen der Thrombolyse die potentiellen Risiken überwiegt.

Die *WAKE UP*[48] und *EXTEND*[49] Studien konnten bei Patienten mit Nachweis eines radiologischen Mismatches zwischen Infarktkern und Penumbra einen möglichen Nutzen der IVT auch bei unklarem Symptombeginn beziehungsweise bis neun Stunden nach Symptombeginn zeigen.

Neben der intravenösen Thrombolyse stellen endovaskuläre Verfahren vor allem bei proximalen Gefäßverschlüssen sehr effektive Behandlungsmöglichkeiten dar. Hierbei besteht technisch zum einen die Möglichkeit der intraarteriellen Thrombolyse[50], zum anderen der mechanischen Rekanalisation durch Thrombusretraktion mittels *Stent-Retrievern*[51, 52] oder durch Thrombusaspiration mittels Aspirationskathetern.[53]

In mehreren unabhängigen randomisierten Studien konnte der Vorteil der mechanischen Rekanalisation mittels *Stent-Retrievern* im Vergleich zu alleiniger Lysetherapie innerhalb eines Zeitraums von sechs Stunden nach Symptombeginn gezeigt werden.[51, 54-57]

Weitere Studien wie *DAWN*[58] und *DEFUSE III*[59] legen zudem bei ausgewählten Patienten die Wirksamkeit der EVT auch in einem erweiterten Zeitfenster bis 16 beziehungsweise bis 24 Stunden nach Symptombeginn nahe.

Die *American Heart Association / American Stroke Association* (AHA/ASA) empfiehlt daher inzwischen die mechanische Rekanalisation mittels *Stent-Retrievern* zusätzlich zur intravenösen Thrombolyse. Sie schloss sich 2018 mit ihren Empfehlungen den obengenannten Studien an und erweiterte für ein bestimmtes Patientenkollektiv das Zeitfenster für eine mechanische Rekanalisation auf bis zu 24 Stunden nach Symptombeginn.[60]

Neben des verbesserten Outcomes ist hervorzuheben, dass die endovaskuläre Therapie auch bei Patienten mit Kontraindikationen für eine systemische Thrombolyse durchgeführt werden kann.

Aktuell bleibt die Therapieoption der EVT jedoch größeren Schlaganfallzentren vorbehalten. Konzepte, welche einen flächendeckenden Zugang zu dieser Behandlung ermöglichen sollen, wie *Telestroke*-Netzwerke[61] und *drip and ship*-Strategien[62], sind Gegenstand aktueller Forschung.

4.5 Bildgebung des akuten Schlaganfalls

Entscheidend in der Diagnostik des akuten Schlaganfalls ist die zerebrale Bildgebung. Grundsätzlich sind sowohl die Computertomographie (CT) als auch Magnetresonanztomographie (MRT) geeignet.

Dabei dient meist die CT der Routinediagnostik, da sie weitreichend verfügbar und schnell durchzuführen ist. Die MRT kommt bei speziellen Fragestellungen, unklarem Symptombeginn oder bei jungen Patienten zum Einsatz.[63]

In vielen Kliniken haben sich in der Schlaganfalldiagnostik inzwischen multiparametrische CT-Protokolle bestehend aus nativer Computertomographie (*non contrast computed tomography,* NCCT), CT-Angiographie (CTA) und CT-Perfusion (CTP) etabliert. Hiermit lassen sich neben dem Blutungsausschluss auch Gefäßverschlüsse und funktionelle Informationen visualisieren, woraus sich wichtige prognostische und therapeutische Konsequenzen ableiten lassen. Dabei ist jedoch wichtig, dass die Bildgebung die Therapie des Schlaganfalls nicht verzögern darf. Eine schnelle Akquisition, Rekonstruktion und Auswertung sind somit essenziell.[60]

4.5.1 Native Computertomographie

Die native Computertomographie ist die Basis der Schlaganfalldiagnostik. Sie erlaubt einen zuverlässigen Ausschluss beziehungsweise die exakte Darstellung intrazerebraler Blutungen.[64] Dies ist entscheidend, da aufgrund der klinischen Symptomatik ein ischämischer Infarkt nicht von einer Blutung zu unterscheiden ist, beide Entitäten jedoch grundsätzlich unterschiedlich therapiert werden müssen.

Weiterhin lassen sich mit der NCCT frühe Infarktzeichen, wie Thrombuskontrast[65, 66], frühe Hypodensitäten oder ein Verlust der Mark-Rinden-Differenzierung darstellen.[66-70] Beim akuten Mediainfarkt lässt sich mittels NCCT durch Unterteilung des Mediastromgebiets in zehn Regionen der *Alberta Stroke Program Early CT Score* (ASPECTS) erheben. Die Punktzahl des Scores korreliert dabei mit dem nachfolgendem Gewebeschaden und dem funktionellen Outcome.[71]

4.5.2 CT-Angiographie

Die CT-Angiographie erlaubt nach Gabe eines Röntgenkontrastmittels die Darstellung der extra- und intrakraniellen Hirngefäße. Mittels CTA lassen sich Gefäßverschlüsse als Kontrastmittelaussparung darstellen. Durch die Identifikation proximal gelegener Gefäßverschlüsse können Patienten für eine mechanische Rekanalisation selektiert werden.

Weiterhin erlaubt die CTA die Darstellung der Kollateralversorgung im Infarktgebiet, welche wichtige prognostische Hinweise für die Schlaganfallbehandlung liefert.[72-75]

4.5.3 CT-Perfusion

Bei der CT-Perfusion handelt es sich um eine funktionelle Bildgebung, die der Darstellung der Hirndurchblutung dient. Nach intravenöser Gabe eines Kontrastmittelbolus erfolgen in Niedrigdosistechnik serielle CT-Aufnahmen des Gehirns zur Darstellung der Kontrastmitteldynamik. Da ein proportionaler Zusammenhang zwischen Kontrastmittel-Anreicherung und Röntgenschwächung in den Gefäßen (gemessen in *Hounsfield-Units,* HU) besteht[76], lässt sich die Kontrastmitteldynamik als Schwächungs-Zeitkurve (*time-attenuation-curve,* TAC) für ein arterielles (*arterial input function*) und ein venöses (*venous output function*) Gefäß, sowie jedes einzelne Voxel darstellen.[63] Die TAC erlaubt eine Berechnung des zerebralen Blutvolumens (*cerebral blood volume,* CBV) und der mittleren Passagezeit (*mean transit time,* MTT). Der CBF lässt sich gemäß des central volume principle aus den beiden obengenannten berechnen. Es besagt: *CBF = CBV/MTT.*

Weitere zeitbasierte Parameter, wie Zeit bis zum Kontrastmittelmaximum (*time to peak,* TTP) und die Zeit bis zum Kontrastmittelabfluss (*time to drain,* TTD) können ohne weiterführende Algorithmen direkt aus der TAC abgelesen werden.[77]

Zur erleichterten Interpretation werden diese Parameter farblich kodiert als sogenannte Perfusionsmaps zur Darstellung gebracht.

Mittels Perfusionsmaps gelingt die Visualisierung eines ischämischen Hirninfarktes als Perfusionsdefizit und weiterhin die Abgrenzung zu anderen *stroke mimics* wie Epilepsie, transient ischämischer Attacke (TIA) oder Migräne, welche keine Perfusionsdefizite zeigen.[78]

Weiterhin erlaubt die CTP eine differenzierte Darstellung von Infarktkern und Penumbra. Man geht davon aus, dass sich innerhalb der Penumbra eine verlängerte MTT mit leicht reduziertem CBF und normalem bis kompensatorisch erhöhtem CBV zeigt, wohingegen sich im Infarktkern eine verlängerte MTT mit stark erniedrigtem CBF und CBV findet.[79, 80] Dies spiegelt die zuvor beschriebene Pathophysiologie des ischämischen Schlaganfalls wider.

Mittels CTP steht somit eine schnelle und zuverlässige Methode zur Identifikation von Infarktkern und Penumbra als Mismatch verschiedener Perfusionsmaps zur Verfügung.[81-83]

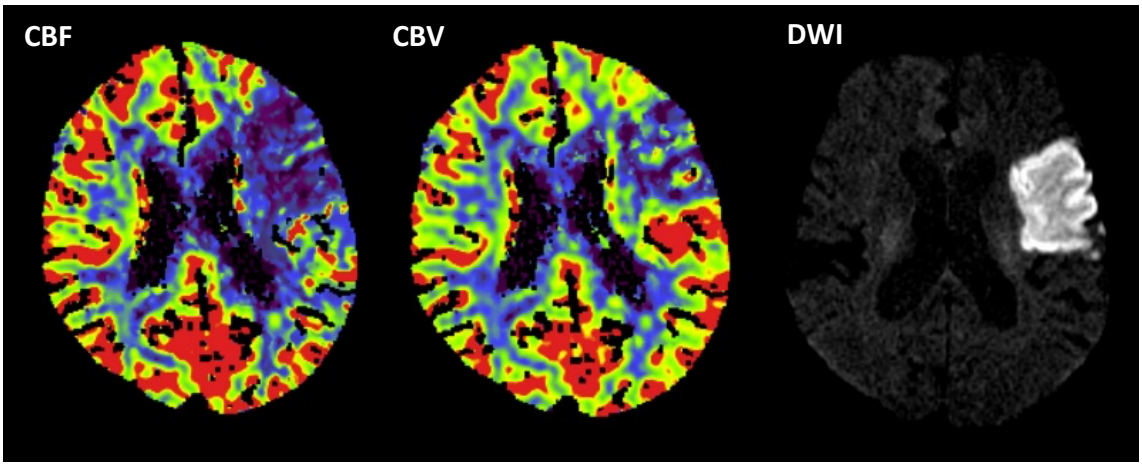

Abbildung 1 CTP und MRT einer 76-jährigen Patientin mit akuter rechtsseitiger brachiofazialer Hemiparese und Aphasie. Man erkennt einen deutlichen Mismatch zwischen zerebralen Blutfluss (CBF) und zerebralen Blutvolumen (CBV) in der CTP. Das finale Infarktvolumen wird mittels Diffusionswichtung (DWI) in der MRT (hier 5 Tage nach der initialen multiparametrischen CT) dargestellt.

Mehrere Studien ergaben, dass durch die zusätzliche Durchführung der CTP die Vorhersagekraft der initialen Diagnostik hinsichtlich des finalen Infarktvolumens und des funktionellen Outcomes nach ischämischem Schlaganfall verbessert werden kann.[72, 84-86]

Weiterhin haben große Studien wie *WAKE UP*, *DAWN* und *DEFUSE III* gezeigt, dass der Mismatch zwischen Infarktkern und Penumbra als wichtige Entscheidungsgrundlage für die Applikation intravenöser Thrombolyse[48] oder Durchführung einer mechanischen Rekanalisation[58, 59] dienen kann.

Ergebnisse erster Studien legen zudem nahe, dass die CT-Perfusion auch zur Darstellung hämodynamischer Besonderheiten, wie zum Beispiel bei hypoplastischer Arteria vertebralis, dienen kann.[87] Weitere Perfusionsphänomene wie die gekreuzt zerebelläre Diaschisis (*crossed cerebellar diaschisis,* CCD)[88, 89] oder die ipsilaterale thalamische Diaschisis[90-92] sind weitreichend bekannt, ihre Auswirkungen auf das Outcome beim ischämischen Schlaganfall bleiben bisher jedoch unklar.

4.6 Zielsetzung der Forschungsarbeiten

Die vorliegende Forschungsarbeit beschäftigt sich mit der multiparametrischen Computertomographie und ihrer Rolle zur Prädiktion des Outcomes beim ischämischen Schlaganfall der vorderen Strombahn. Aus einem Kollektiv von über 1500 Patienten mit vermutetem Schlaganfall und in der Akutsituation durchgeführter multiparametrischer CT über einen Zeitraum von fünf Jahren wurden mehrere Subkollektive gebildet und analysiert. Besonderes Augenmerk wurde hierbei auf die bildmorphologische Darstellung von Kollateralen und der gekreuzt zerebellären Diaschisis mittels CT-Angiographie und CT-Perfusion, sowie auf deren Einfluss auf das morphologische und funktionelle Outcome nach ischämischem Schlaganfall gelegt.

4.6.1 Gekreuzt zerebelläre Diaschisis

Unter gekreuzt zerebellärer Diaschisis versteht man die verminderte Perfusion und den reduzierten Metabolismus in der kontralateralen Kleinhirnhemisphäre infolge einer supratentoriellen Dysfunktion.[93-95] Dieses Phänomen wurde im Rahmen von Hirntumoren[96], Epilepsie[97], Enzephalitis[98] sowie nach Schlaganfällen beobachtet.[99-101]

Man geht davon aus, dass die CCD auf einer verminderten Aktivierung zerebellärer Neurone durch reduzierte exzitatorische Einflüsse aus dem corticopontocerebellärem Trakt basiert.[102] Beim ischämischen Schlaganfall durch einen proximalen Gefäßverschluss der vorderen Strombahn konnte eine CCD in etwa einem Drittel der Fälle nachgewiesen werden.[89, 103]

Einige Studien suggerieren, dass eine CCD über mehrere Jahre bestehen und infolgedessen zu degenerativen Veränderungen im Gehirn führen kann.[88, 104-106] Zudem existieren Studien, die einen Zusammenhang der zerebellären Minderperfusion[100] und des generellen Auftretens einer CCD mit dem funktionellen Outcome beim Schlaganfall gezeigt haben.[107]

Ziel unserer Arbeit war es daher, den Einfluss der CCD auf das morphologische und funktionelle Outcome von Patienten mit akutem ischämischem Schlaganfall infolge eines Gefäßverschlusses der vorderen Strombahn zu analysieren.

4.6.2 Leptomeningeale Kollateralen

Zerebrale Kollateralen spielen eine wichtige Rolle in der Pathophysiologie des ischämischen Schlaganfalls, da sie für die Versorgung der Penumbra innerhalb des ischämischen Gehirnareals mitverantwortlich sind. Sie bestimmen somit die neurologische Symptomatik und das finale Infarktvolumen eines Schlaganfalls.[108, 109]

Man unterscheidet primäre und sekundäre arterielle Kollateralen im Gehirn. Die primären Kollateralen werden von Arterien des Circulus arteriosus Willisii gebildet und können als vorbestehende Anastomosen die direkte Versorgung einer ischämischen Region sicherstellen. Sekundäre Kollateralen werden vor allem von den leptomeningealen Arterien gebildet und entwickeln sich im Verlauf einer Ischämie. Sie spielen für die Perfusion der Penumbra beim Schlaganfall eine wichtige Rolle.[108-110] Kollateralen können folglich sowohl die Schwere als auch den zeitlichen Verlauf eines ischämischen Schlaganfalls beeinflussen.[110, 111]

Mehrere Studien weisen darauf hin, dass gut ausgebildete Kollateralen mit dem Erfolg der endovaskulären Rekanalisation[112, 113] sowie der intravenösen Thrombolyse[114-117] korrelieren. Eine gute Kollateralversorgung ist somit für das funktionelle Outcome nach ischämischem Schlaganfall entscheidend.[112, 115, 118] Leptomeningeale Kollateralen spielen daher in der Entscheidung über die optimale Therapie beim akuten Schlaganfall eine wichtige Rolle.[118]

Während es bereits viele Studien zum Einfluss von Kollateralen auf den Therapieerfolg beim akuten Schlaganfall gibt, ist die Datenlage zum Verlauf bei Patienten, die einzig eine supportive Behandlung erhielten, bisher gering.

Ziel unserer Arbeit war es, den Einfluss zerebraler Kollateralen auf das morphologische und funktionelle Outcome in den beiden Subgruppen, welche entweder eine intravenöse Thrombolyse (IVT-Gruppe) oder eine supportive Therapie (non-IVT-Gruppe) erhalten haben, zu vergleichen.

5 Zusammenfassung / Summary

Zusammenfassung

Der Schlaganfall ist eine aus sozioökonomischer und gesundheitspolitischer Sicht bedeutende Erkrankung. Durch verbesserte Behandlungsmöglichkeiten in einer gleichzeitig alternden Gesellschaft gibt es immer mehr Überlebende, die mit den Folgen eines Schlaganfalls leben müssen.[1, 2] Zudem stellen neben den bisherigen starren Zeitfenstern zunehmend radiologische Selektionskriterien eine mögliche Grundlage zur Therapieentscheidung dar.[48, 58, 59] Es ist demnach von großem Interesse, mögliche Einflussgrößen auf das Outcome nach ischämischem Schlaganfall zu identifizieren. Ziel dieser Forschungsarbeit ist es, anhand bildmorphologischer Parameter in der CT-Angiographie und CT-Perfusion Rückschlüsse auf das morphologische und funktionelle Outcome bei Patienten mit ischämischem Schlaganfall zu ziehen.

I.) Gekreuzt zerebelläre Diaschisis

Unter gekreuzt zerebellärer Diaschisis (*crossed cerebellar diaschisis*, CCD) versteht man die verminderte Perfusion und den reduzierten Metabolismus der kontralateralen Kleinhirnhemisphäre infolge einer supratentoriellen Dysfunktion.[93-95] Dieses Perfusionsphänomen kann bei circa einem Drittel aller Schlaganfälle der vorderen Strombahn mit nachgewiesenem Gefäßverschluss beobachtet werden.[89, 103]

Ziel dieser Arbeit war es, den Einfluss der CCD auf das morphologische und funktionelle Outcome zu untersuchen. Mittels Regressionsanalyse konnte gezeigt werden, dass das Auftreten einer CCD weder mit dem morphologischen noch dem funktionellen Outcome nach Schlaganfall assoziiert war. Diese Ergebnisse decken sich mit vorherigen Studien, welche die Diaschisis als reversibel beschreiben.[119]

Als sekundärer Outcomeparameter konnte ein gehäuftes Auftreten des Parenchymhämatoms (*parenchymal hematoma*, PH) bei Vorliegen einer CCD beobachtet werden.

Unsere Studie liefert wichtige Erkenntnisse zur Einordnung der CCD in der klinisch-radiologischen Routinebefundung. Die Assoziation von CCD und PH ist beachtenswert und bedarf weitergehender Forschung.

II.) Leptomeningeale Kollateralen

Leptomeningeale Kollateralen spielen eine wichtige Rolle beim ischämischen Schlaganfall, da sie durch die Versorgung der Penumbra einen direkten Einfluss auf die Infarktgröße und somit auf das funktionelle Outcome haben.[73, 111, 114, 116, 120-122]

In dieser Arbeit beschäftigten wir uns vor allem mit der unterschiedlichen Bedeutung leptomeningealer Kollateralen für (a) Patienten, die eine intravenöse Thrombolyse (IVT Gruppe) erhalten und (b) Patienten, die lediglich eine supportive Therapie erhalten (non-IVT Gruppe) haben.

Mittels *Propensity Score Matching* und anschließender Regressionsanalyse konnten gut ausgebildete Kollateralen sowohl als unabhängige Prädiktoren eines geringeren finalen Infarktvolumens als auch eines guten funktionellen Outcomes identifiziert werden, sofern eine Thrombolyse durchgeführt wurde. In der non-IVT Gruppe konnte hingegen mittels Kollateralstatus keine signifikante Aussage bezüglich des Outcomes getroffen werden.

Unsere Ergebnisse unterstreichen die Bedeutung der IVT für ein günstiges Outcome, insbesondere bei Patienten mit gut ausgebildeten Kollateralen. Weiterhin konnten wir zeigen, dass leptomeningeale Kollateralen eine geringe prognostische Bedeutung für den Verlauf des ischämischen Schlaganfalls haben, wenn keine Reperfusionstherapie durchgeführt werden kann.

Summary

Stroke depicts an important socio-economic disease with a considerable public health impact. Due to an ageing society and improved treatment the number of people surviving or living with the consequences after stroke is continuously rising.[1, 2] Furthermore, radiologic patient assessment gains more and more importance over rigid time windows for therapeutic decision making in stroke.[48, 58, 59] Therefore, it is of great interest to identify possible influencing variables on the outcome after ischemic stroke. The aim of this research project is to obtain radiologic parameters using CT angiography and CT perfusion imaging that provide prognostic information on morphologic and functional outcome in acute ischemic stroke.

I.) Crossed cerebellar diaschisis

Crossed cerebellar diaschisis (CCD) describes the reduced perfusion and metabolism of the contralateral cerebellar hemisphere caused by a supratentorial dysfunction.[93-95] This phenomenon is observed in about one third of all ischemic strokes due to large anterior circulation occlusion.[89, 103]

The aim of this study was to demonstrate the influence of CCD on the morphologic and functional outcome in large anterior circulation occlusion. Using regression analysis, it was shown that the occurrence of CCD was associated with neither morphologic nor functional outcome in ischemic stroke. The results are in line with former studies describing diaschisis as a reversible condition.[119]

A significant association between parenchymal hematoma (PH) and CCD was noted as secondary outcome measurement.

Our study provides important findings on the relevance of CCD in routine diagnostics. The association of CCD and PH is noteworthy and requires further research.

II.) Leptomeningeal collaterals

Leptomeningeal collateral circulation plays an important role in ischemic stroke, as the blood supply to the penumbral regions influences both final infarction volume and functional outcome.[73, 111, 114, 116, 120-122]

In this study, we focused on the differential effects of cerebral collaterals for patients receiving either thrombolysis (IVT group) or receiving supportive care (non-IVT group).

Using Propensity Score Matching and subsequent regression analysis we identified good collaterals as independent predictor of smaller final infarction volume as well as good functional outcome when thrombolysis was performed. In the non-IVT group collateral status was not able to predict the outcome significantly.

Our results underline the importance of IVT regarding a favorable outcome especially in patients with good collateral circulation. Moreover, we could demonstrate the reduced prognostic value of leptomeningeal collaterals in ischemic stroke if thrombolysis is not performed.

6 Originalarbeiten

6.1 Veröffentlichung I: Crossed cerebellar diaschisis in acute ischemic stroke: Impact on morphologic and functional outcome

Kunz, Wolfgang G.; Sommer, Wieland H.; Hoehne, Christopher; Fabritius, Matthias P.; **Schuler, Felix**; Dorn, Franziska; Othman, Ahmed E.; Meinel, Felix G.; von Baumgarten, Louisa; Reiser, Maximilian F.; Ertl-Wagner, Birgit; Thierfelder, Kolja M.

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Crossed cerebellar diaschisis in acute ischemic stroke: Impact on morphologic and functional outcome

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Abstract

Crossed cerebellar diaschisis (CCD) is the phenomenon of hypoperfusion and hypometabolism of the contralateral cerebellar hemisphere caused by dysfunction of the related supratentorial region. Our aim was to analyze its influence on morphologic and functional outcome in acute ischemic stroke. Subjects with stroke caused by a large vessel occlusion of the anterior circulation were selected from an initial cohort of 1644 consecutive patients who underwent multiparametric CT including whole-brain CT perfusion. Two experienced readers evaluated the posterior fossa in terms of CCD absence (CCD−) or presence (CCD+). A total of 156 patients formed the study cohort with 102 patients (65.4%) categorized as CCD− and 54 (34.6%) as CCD+. In linear and logistic regression analyses, no significant association between CCD and final infarction volume ($\beta = -0.440$, $p = 0.972$), discharge mRS ≤ 2 (OR = 1.897, $p = 0.320$), or 90-day mRS ≤ 2 (OR = 0.531, $p = 0.492$) was detected. CCD+ patients had larger supratentorial cerebral blood flow deficits (median: 164 ml vs. 115 ml; $p = 0.001$) compared to CCD−patients. Regarding complications, CCD was associated with a higher rate of parenchymal hematomas (OR = 4.793, $p = 0.035$). In conclusion, CCD is frequently encountered in acute ischemic stroke caused by large vessel occlusion of the anterior circulation. CCD was associated with the occurrence of parenchymal hematoma in the ipsilateral cerebral infarction but did not prove to significantly influence patient outcome.

Keywords

Acute stroke, brain recovery, cerebral blood flow, intracranial hemorrhage, neuroradiology

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Introduction

Crossed cerebellar diaschisis (CCD) is the phenomenon of a decreased cerebellar perfusion and glucose metabolism secondary to a supratentorial malfunction of brain tissue in the contralateral hemisphere, first described by Baron et al.[1–3] It can be detected through changes in electrical activity, cerebral blood flow, or cerebral metabolic rates for glucose and oxygen using methods such as electroencephalography, single-photon emission-computed tomography (SPECT), or positron emission tomography (PET).[4,5] CCD has been reported in supratentorial tumors,[6] epilepsy,[7] encephalitis,[8] and cerebral infarction.[9] Animal studies suggest that CCD is explained by deactivation of cerebellar neurons caused by reduction of excitatory impulses via the corticopontocerebellar tract.[5,10] In

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ischemic stroke, CCD has been observed during the acute, subacute, and chronic phase.[11,12] Current scientific concepts attribute acute CCD to functional neuronal deafferentiation, whereas chronic CCD probably reflects a state of transneuronal degeneration.[13] In ischemic stroke due to large anterior circulation vessel occlusion, CCD has been shown to be present in about one-third of the affected patients in the acute phase.[14,15]

While the original definition of CCD was based on the idea that it is a transient condition,[16] several publications have reported CCD up to decades after the index stroke.[17–20] Regarding the reversibility of CCD, however, several serial SPECT and PET studies demonstrated that some patients show complete reversal of CCD during follow-up.[11,13,21–23] With respect to functional outcome, the majority of studies in stroke patients using SPECT or PET investigated subacute and chronic CCD, reflecting the fact that these imaging methods are not eligible to routinely assess perfusion in the acute stroke setting. Several studies with relatively small sample sizes report correlations with clinical severity scales for subacute[11,13,24,25] and chronic CCD.[26,27] Yet, the two largest studies on subacute CCD report no independent predictive value after statistical correction for the infarct hypoperfusion volume.[28,29] For acute CCD, no correlations to clinical severity scales were established so far.[11,25,26] However, current sample sizes are too small to draw general conclusions regarding its clinical impact.

Unlike SPECT and PET, computed tomography perfusion imaging is a method that reliably demonstrates areas of hypoperfusion in clinical routine stroke workup.[30] Advances in imaging technology meanwhile allow to cover the entire brain tissue at a reasonable radiation dose (whole-brain CT perfusion, WB-CTP).[31] While recent WB-CTP studies on stroke patients have shown the occurrence of CCD in the acute phase to be dependent on the location of the supratentorial perfusion deficit and the severity of supratentorial hypoperfusion,[14] the key question of the clinical impact of CCD in acute ischemic stroke remains unanswered.

Therefore, the aim of the present whole-brain CT perfusion study was to determine the influence of CCD occurrence in the acute phase on morphologic and functional outcome in patients with acute ischemic stroke due to large anterior circulation vessel occlusion.

Material and methods

Study design and population

The institutional review board of the LMU Munich (Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München) approved this retrospective study according to the Helsinki Declaration of 1975 (and as revised in 2013) and waived requirement for informed consent. Our initial cohort consisted of 1644 consecutive patients who had undergone WB-CTP due to suspected stroke between April 2009 and June 2014.

Out of this cohort, we included all subjects with

(1) occlusion of the internal carotid (ICA), carotid T and/or middle cerebral artery (MCA),
(2) perfusion deficit in the MCA territory on WB-CTP, and
(3) follow-up confirmed ischemic infarction.

We excluded patients with

(1) any abnormality of the posterior vasculature on CT angiography (CTA),
(2) cerebellar infarction or other cerebellar pathology on initial or follow-up imaging,
(3) missing follow-up imaging, or
(4) incomplete coverage of the cerebellum or non-diagnostic quality of WB-CTP.

Out of the initial 1644 patients, 323 patients had an ICA, carotid T, or MCA occlusion. Out of these, 20 patients with missing follow-up imaging, 89 with abnormalities of the posterior circulation, 14 with pathologies of the cerebellum, 6 with acute cerebellar infarction on follow-up imaging and 38 with incomplete cerebellar coverage or non-diagnostic quality of WB-CTP were excluded. The remaining 156 patients formed the final study population.

CT acquisition, CT perfusion processing and follow-up imaging

All patients underwent a standardized multiparametric CT protocol consisting of non-enhanced CT (NECT), single-phase CT angiography (spCTA), and WB-CTP. The acquisition protocol has been described in detail before.[32] The source image processing was performed with SYNGO Volume Perfusion CT Neuro software using a semi-automated deconvolution algorithm (Auto Stroke MTT) on a dedicated workstation (Syngo MMWP, VA 21A; Siemens Healthcare, Erlangen, Germany). A series of 31 color-coded slices was generated for each of the hemodynamic parameters cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), time to drain (TTD), and time to peak (TTP). Follow-up imaging was performed with MRI in 56% and NECT in 44% of patients as previously described.[14] The median time from initial WB-CTP imaging to follow-up imaging was two days for MRI (range: 1–49) and one day for NECT (range: 1–16).

Image analysis

The assessment of presence of CCD was performed qualitatively by two independent readers (one neurologist with nine years and one radiologist with seven years of experience in CTP reading, respectively) blinded to all clinical data and the location of supratentorial infarctions by cropping all images to the posterior fossa. In case of disagreement, a consensus was reached in a separate session. Only perfusion anomalies in the cerebellar hemisphere contralateral to the supratentorial lesion were counted as CCD positive. Figure 1 shows representative examples of CCD− and CCD+ patients.

The extent of the supratentorial ischemic region was assessed on NECT using the semi-quantitative Alberta Stroke Program Early Computed Tomography Score (ASPECTS).[33] CBF and CBV deficit volume and final infarction volume were determined as previously described.[31] The primary morphologic outcome parameter was final infarction volume. As secondary morphologic outcome, we determined parameters that represent the morphologic course from ischemia to infarction using an approach comparable to previous studies.[34–37] To quantify the change from the initial hemodynamic impairment to the final infarcted tissue, we used the following calculated parameters as surrogates: [final infarction volume/CBF deficit volume], [final infarction volume/(CBF deficit volume – CBV deficit volume)], and [CBF deficit volume – final infarction volume]. The rationale of these parameters is illustrated in supplementary Figure 1. All available follow-up imaging prior to discharge was assessed for subacute stroke complications. Hemorrhagic infarction and parenchymal hematoma were categorized as type I and II according to the European Cooperative Acute Stroke Study (ECASS) criteria.[38] Parenchymal hematoma type II development has a negative influence on functional outcome.[39] Intracranial hemorrhage (ICH) remote to the infarction area was classified as extraischemic. The presence of space-occupying edema was defined as previously described and assessed using follow-up NECT on day 3 ± 2.[40]

Acute stroke therapy

Intravenous thrombolysis (IVT) was administered to eligible patients at a dose of 0.9 mg/kg bodyweight

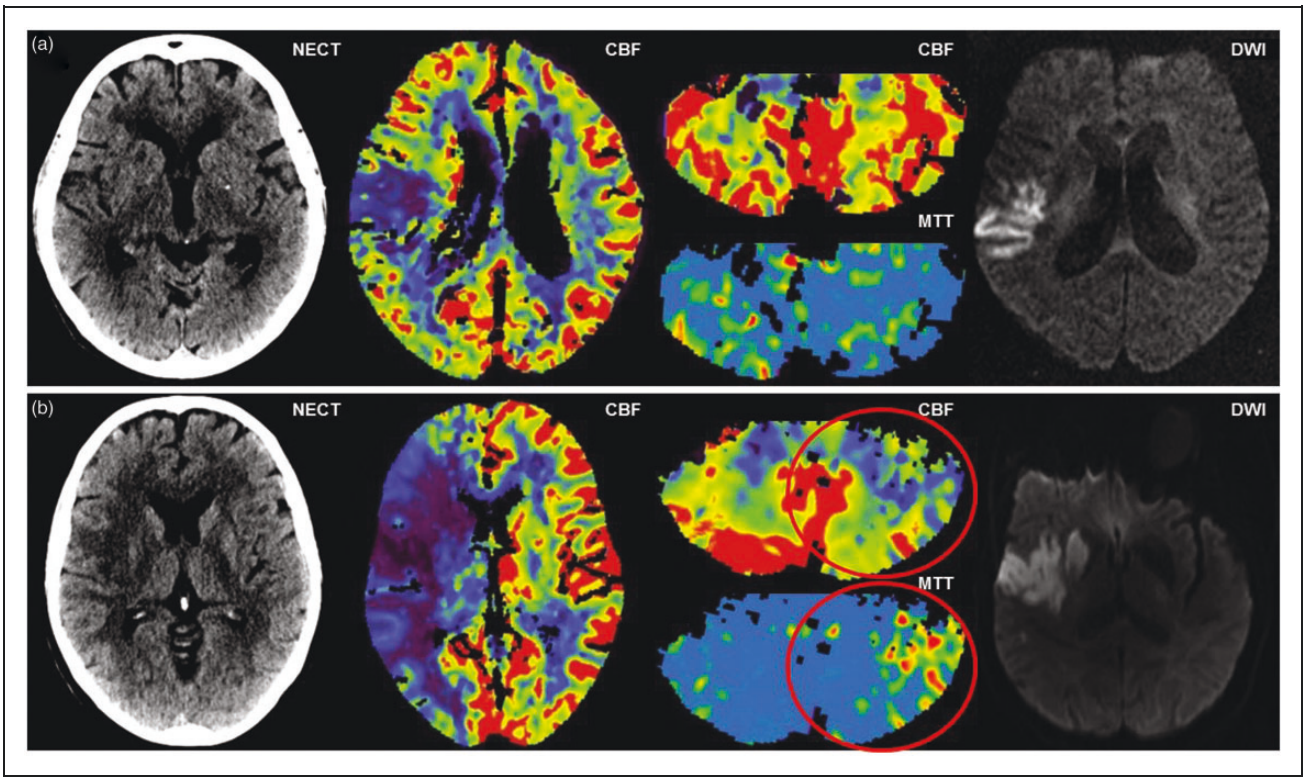

Figure 1. Examples of CCD− and CCD+ patients. Patient examples of acute ischemic stroke without and with signs of crossed cerebellar diaschisis (CCD). NECT, supratentorial CBF map, infratentorial CBF and MTT map, and follow-up DWI are depicted from for a CCD− (a) and a CCD+ patient (b). NECT: non-enhanced CT; CBF: cerebral blood flow; MTT; mean transit time; DWI: diffusion-weighted imaging.

(maximum dose: 90 mg) in two parts: 10% of the total dose was administered as an IV bolus, immediately followed by an IV infusion over 60 min of the remaining dose diluted in 50 ml of sodium chloride 0.9%. IVT was started approximately 10–20 min after imaging evaluation, i.e. time from symptom onset plus 10–20 min. If IVT was given, preexisting antiplatelet or anticoagulation therapy was halted for 24 h.

Endovascular therapy (EVT) was performed as a mechanical stent retriever thrombectomy procedure either under general anesthesia or, whenever deemed appropriate by the interventional neuroradiologist and the anesthesiologist, under conscious sedation. All procedures were performed in a triaxial fashion using a distal access catheter and a microcatheter to deploy a stent retriever device. All used stent retrievers in this cohort were latest generation devices (Solitaire, ev3 Neurovascular, Irvine, CA, USA; Preset, phenox GmbH, Bochum, Germany; Trevo, Concentric Medical, Mountain View, CA, USA). After affirmation of recanalization, the catheter material was removed.

In general, therapy with aspirin (100 mg/day) was initiated immediately after admission to the stroke unit. Exclusion criteria were intracerebral hemorrhage and IVT administration. In case of IVT, aspirin therapy was suspended for at least 24 h and initiated only after repeated imaging to exclude IVT-related hemorrhage. In case of cardioembolic stroke, the decision to start anticoagulation was made individually depending on the size of infarction.

Functional outcome data

The functional outcome evaluation in this study was based on the National Institutes of Health Stroke Scale (NIHSS) score[41] determined on admission and the modified Rankin Scale (mRS) score[42] assessed on admission, on discharge and 90 days after the stroke event. Furthermore, the premorbid mRS score representing patient disability prior to the current stroke event was estimated by taking detailed medical history of the patient whenever possible. Patients were excluded from the functional outcome analysis in case of premorbid mRS > 1, missing clinical documentation, second stroke event, or death to other cause within 90 days. None of the included patients had a history of premorbid ischemic injury to the ipsilateral MCA territory. Detailed characteristics of excluded patients are provided in supplementary Table 1.

Statistical analysis

We performed all statistical analyses using SPSS Statistics 23 (IBM, Armonk/NY, USA). Normal distribution was evaluated using the Kolmogorov–Smirnov test. In case of non-normal distribution, we applied the Chi-squared test for categorical and the Mann–Whitney-U test for continuous variables to identify significant differences between patients classified as CCD+ and CCD−. Univariate linear regression analysis was used to test the association between predictors and continuous morphologic outcome variables. Logistic binary regression analysis was used between predictors and the categorical functional outcome variables. All metric and normally distributed variables are reported as mean ± standard deviation; non-normally distributed variables are presented as median (interquartile range). Categorical variables are presented as frequency and percentage. P values below 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

A total of 156 patients were included for WB-CTP reading and statistical analysis. Mean age was 73 years (IQR: 58–82). Sixty-nine (44%) patients were male. Out of the 156 evaluated patients, 102 were classified CCD negative (65.4%), and 54 (34.6%) CCD positive. CCD+ patients showed significantly larger supratentorial CBF and CBV deficit volumes compared to CCD− patients (each with $p < 0.001$). No statistically significant differences between these two groups were found in terms of time from symptom onset, NIHSS on admission, ASPECTS, final infarction volume, cardiovascular risk factors or etiology of stroke (each with $p > 0.05$). Simply comparing the two groups, CCD+ patients had worse discharge mRS scores ($p = 0.008$). Detailed characteristics of CCD+ and CCD− patients are shown in Table 1.

Association of CCD with morphologic outcome

For the analysis of morphologic outcome, all 156 patients were included. In the linear regression analysis, no statistically significant associations were evident between the presence of CCD and any of the morphologic outcome parameters (each with $p > 0.05$). Results are shown in Table 2. Additional per-patient plots of CBF deficit and final infarction volume stratified for treatment groups and CCD status are provided in supplementary Figure 2.

Association of CCD with functional outcome

According to our exclusion criteria for the analysis of functional outcome, we excluded patients with premorbid mRS > 1 (N = 16), missing documentation (N = 5),

Table 1. Characteristics of CCD− and CCD+ acute ischemic stroke patients.

	Overall (N = 156)	CCD− (n = 102)	CCD+ (n = 54)	*p*
Patient data				
Age	73 (58–82)	72 (55–81)	74 (67–82)	0.069
Male sex	69 (44.2%)	45 (44.1%)	24 (44.4%)	0.969
Time from symptom onset	153 (103–282)	164 (103–301)	147 (98–268)	0.658
NIHSS on admission	14 (9–17)	13 (8–16)	15 (11–17)	0.108
Treatment				
IV thrombolysis	102 (66.7%)	64 (64.6%)	38 (70.4%)	0.473
Endovascular therapy	57 (37.3%)	37 (37.4%)	20 (37.0%)	0.996
Imaging				
ASPECTS	9 (7–10)	9 (7–10)	9 (7–9)	0.163
Occluded vessels				
ICA	57 (36.5%)	39 (38.2%)	18 (33.3%)	0.545
Carotid T	13 (8.3%)	9 (8.8%)	4 (7.4%)	0.761
M1 segment of MCA	87 (55.8%)	55 (53.9%)	32 (59.3%)	0.523
M2 segment of MCA	35 (22.4%)	23 (22.5%)	12 (22.2%)	0.963
M3 segment of MCA	6 (3.8%)	4 (3.9%)	2 (3.7%)	0.946
CBF deficit volume	133 (86–191)	115 (67–181)	164 (123–205)	**0.001**
CBV deficit volume	43 (12–87)	25 (8–83)	50 (28–95)	**0.007**
CBF-CBV mismatch %	65 (39–85)	65 (39–89)	64 (42–79)	0.456
Final infarction volume	33 (10–85)	23 (7–83)	53 (12–122)	0.106
Functional outcome				
Premorbid mRS	0 (0–0)	0 (0–0)	0 (0–0)	0.936
Admission mRS	5 (4–5)	5 (4–5)	5 (4–5)	0.762
Discharge mRS	4 (3–5)	4 (2–5)	5 (4–5)	**0.008**
90-day mRS	4 (1–6)	3 (1–5)	4 (3–6)	0.183
Cardiovascular risk factors				
Hypertension	105 (70.0%)	66 (68.0%)	39 (73.6%)	0.479
Atrial fibrillation	73 (48.7%)	45 (46.4%)	28 (52.8%)	0.451
Diabetes mellitus	27 (18.0%)	14 (14.4%)	13 (24.5%)	0.124
Smoking	38 (25.3%)	26 (26.8%)	12 (22.6%)	0.575
Hypercholesteremia	48 (32.0%)	29 (29.9%)	19 (35.8%)	0.455
Etiology of stroke				
Cardioembolic	80 (53.3%)	49 (50.5%)	31 (58.5%)	0.349
Arterio-arterial	38 (25.3%)	24 (24.7%)	14 (26.4%)	0.822
Other	17 (11.3%)	14 (14.4%)	3 (5.7%)	0.105
Unknown	17 (11.3%)	10 (10.3%)	7 (13.2%)	0.592
Complications				
Hemorrhagic infarction				0.363
Type 1	26 (16.7%)	14 (13.7%)	12 (22.2%)	
Type 2	18 (11.5%)	13 (12.7%)	5 (9.3%)	
Parenchymal hematoma				**0.026**
Type 1	12 (7.7%)	5 (4.9%)	7 (13.0%)	
Type 2	2 (1.3%)	0 (0.0%)	2 (3.7%)	
Extraischemic ICH	9 (5.8%)	6 (5.9%)	3 (5.6%)	0.934
Space-occupying edema	30 (19.2%)	19 (18.6%)	11 (20.4%)	0.793

CCD: crossed cerebellar diaschisis; NIHSS: national institutes of health stroke scale; ASPECTS: Alberta stroke program early CT score; ICA: internal carotid artery; MCA: middle cerebral artery; CBF/CBV: cerebral blood flow/volume; mRS: modified Rankin Scale; ICH: intracranial hemorrhage. Note: Values presented are count (percentage) for categorical and median (interquartile range) for ordinal or continuous variables. Proportion analysis tests for categorical variables were performed using the χ^2 test. Nonparametric tests for non-normally distributed continuous variables were performed using the Mann–Whitney U test, and for ordinal variables using the independent samples median test. Time parameters are measured in minutes; volume parameters are measured in mL. Bold p values indicate statistical significance.

Table 2. Predictors of morphologic and functional outcome.

Morphologic outcome	Final infarction[a]		Final infarction/ CBF deficit[a]		Final infarction/ Penumbra[a,b]		CBF deficit – Final infarction[a]	
Independent variables	β	p	β	p	β	p	β	p
Age	−0.660	0.116	−0.002	0.593	−0.059	**0.018**	0.660	0.116
Sex	3.331	0.787	0.011	0.931	0.651	0.373	−3.331	0.787
NIHSS on admission	2.127	**0.032**	0.011	0.295	0.012	0.843	−2.127	**0.032**
ASPECTS	−6.410	0.061	−0.037	0.298	−0.137	0.496	6.410	0.061
CBF deficit volume	−0.214	0.162	−0.003	0.054	−0.012	0.192	1.214	<**0.001**
CBV deficit volume	1.410	<**0.001**	0.001	0.748	0.018	0.309	−1.410	<**0.001**
CBF-CBV mismatch %	0.795	0.125	−0.008	0.119	−0.061	**0.048**	−0.795	0.125
IV thrombolysis	9.815	0.440	−0.017	0.895	1.186	0.116	−9.815	0.440
Endovascular therapy	−48.198	<**0.001**	−0.202	0.090	−1.301	0.054	48.198	<**0.001**
CCD	−0.440	0.972	0.004	0.975	−0.437	0.552	0.440	0.972

Functional outcome	Admission mRS ≤ 2[c]		Discharge mRS ≤ 2[c]		Discharge mRS ≤ 4[c]		90-day mRS ≤ 2[c]	
Independent variables	OR	p	OR	p	OR	p	OR	p
Age	1.046	0.303	0.966	0.070	0.997	0.880	0.963	0.269
Sex	0.167	0.244	0.402	0.098	0.546	0.224	0.630	0.553
NIHSS on admission	0.438	**0.008**	0.823	**0.003**	0.905	**0.033**	0.782	**0.041**
ASPECTS	0.557	0.394	1.009	0.963	0.825	0.204	0.960	0.917
CBF deficit volume	0.983	0.321	0.998	0.761	0.995	0.441	1.009	0.462
CBV deficit volume	1.070	0.145	0.978	0.243	0.989	0.459	0.983	0.564
CBF-CBV mismatch %	1.099	0.152	0.961	0.114	0.997	0.878	0.987	0.756
Final infarction volume	0.981	0.285	0.983	0.059	0.990	**0.022**	0.895	**0.026**
IV thrombolysis	2.207	0.615	10.400	**0.003**	1.704	0.327	1.512	0.662
Endovascular therapy	3.080	0.507	0.426	0.120	1.086	0.857	1.300	0.748
CCD	1.703	0.789	1.897	0.320	0.611	0.313	0.531	0.492

[a]All parameters represent volumetric measures.
[b]Penumbra is defined as CBF deficit volume – CBV deficit volume.
[c]Available data: Admission mRS 131/131, Discharge mRS 131/131, 90-day mRS 72/131.
mRS: modified Rankin Scale; NIHSS: national institutes of health stroke scale; ASPECTS: Alberta stroke program early CT score; CBF / CBV: cerebral blood flow/volume; OR: odds ratio. Note: A univariate linear regression analysis was performed for the indicated morphologic outcome parameters for the complete study population of 156 patients. A binary logistic regression analysis was performed for the indicated functional outcome parameters for the patient selection according to Figure 2. Bold p values indicate statistical significance.

second stroke events within 90 days (N = 2), and death to non-stroke-related causes within 90 days (N = 2). A flow chart of the patient selection is presented in Figure 2. Bar graphs representing admission, discharge, and 90-day mRS scales are shown in Figure 3.

In the binary logistic regression analysis, no statistically significant associations between CCD and functional outcome parameters were evident (each with $p > 0.05$). Higher NIHSS scores on admission and larger final infarction volume had significant negative associations with favorable outcome parameters, and the administration of IV thrombolysis had a significant positive association with favorable discharge mRS. Results are presented in Table 2. Additional per-patient mRS data plots stratified for treatment groups and CCD status are provided in supplementary Figure 3.

Association of CCD with subacute stroke complications

In the binary logistic regression analysis, the occurrence of parenchymal hematoma showed a significant association with the presence of CCD. CCD was not associated with the occurrence of hemorrhagic infarction, extraischemic intracranial hemorrhage, or the development of space-occupying edema. The results are presented in Table 3. The results from a regression analysis for parenchymal hematoma development

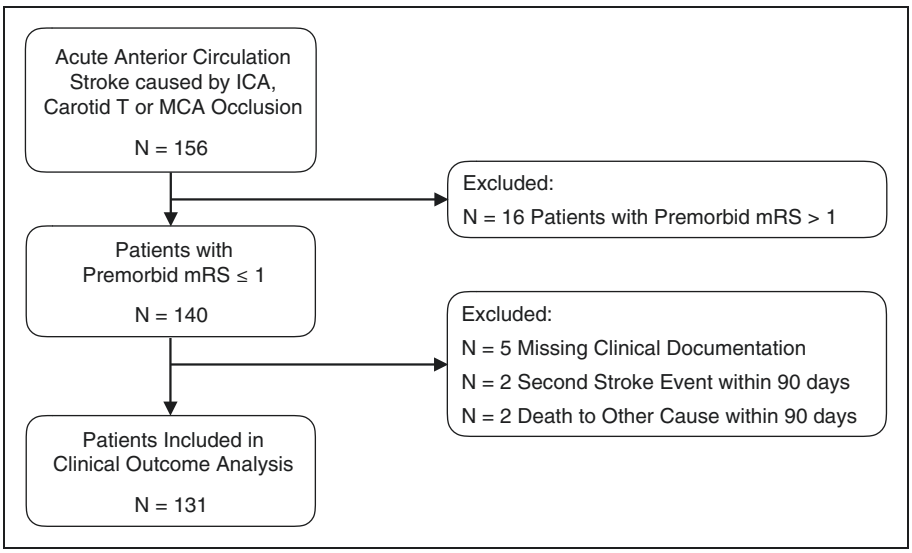

Figure 2. Flow chart of patient selection for functional outcome analysis.
ICA: internal carotid artery; MCA: middle cerebral artery; mRS: modified Rankin Scale.

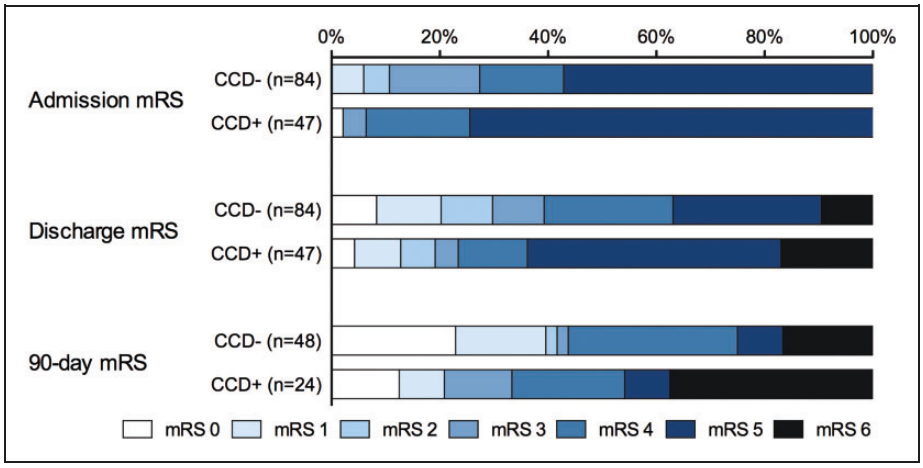

Figure 3. Modified Rankin Scale scores of CCD− and CCD+ patients.
CCD: crossed cerebellar diaschisis; mRS: modified Rankin Scale.

which additionally incorporates further quantitative CT perfusion parameters are provided in supplementary Table 2.

Discussion

In our study on patients with acute ischemic stroke due to an anterior circulation occlusion, the presence of CCD as assessed by WB-CTP in the acute phase showed no independent association with morphologic and functional patient outcome. Among the most common complications after acute ischemic stroke, the occurrence of parenchymal hematoma was associated with the presence of CCD.

CCD in the setting of ischemic stroke has mainly been studied in the subacute and chronic phase[25,28,29]. Although only few studies compared the phase-specific clinical implications of CCD,[25] the results suggest a negative impact of subacute and chronic CCD, but not acute CCD, on functional outcome.[11,26] As possible associations between the presence of CCD with both functional outcome and complications in acute ischemic stroke are controversial,[28,29] our study makes an important contribution to the significance of CCD as it is the first CT perfusion study on the clinical impact of acute CCD. Recent studies on CCD occurrence and perfusion characteristics suggest that CT perfusion is an appropriate technique to study the phenomenon of CCD.[14,15]

Table 3. Predictors of subacute stroke complications.

	Hemorrhagic infarction		Parenchymal hematoma		Extraischemic ICH		Space-occupying edema	
Independent variables	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Age	1.008	0.605	1.016	0.586	0.984	0.567	0.966	0.184
Sex	0.611	0.284	0.455	0.287	1.094	0.916	0.982	0.982
NIHSS on admission	1.095	**0.023**	1.024	0.703	1.047	0.539	1.146	0.059
ASPECTS	0.943	0.641	1.002	0.992	1.051	0.838	0.845	0.373
CBF deficit volume	1.001	0.907	1.001	0.934	0.989	0.358	0.970	**0.046**
CBV deficit volume	0.978	0.104	1.007	0.693	1.020	0.368	1.038	0.121
CBF-CBV mismatch %	0.969	0.129	1.005	0.877	1.028	0.434	1.035	0.309
Final infarction volume	1.009	**0.006**	0.998	0.659	1.002	0.780	1.021	**<0.001**
IV thrombolysis	2.096	0.174	1.869	0.484	4.123	0.239	0.217	0.059
Endovascular therapy	2.478	**0.043**	0.693	0.602	0.450	0.410	3.412	0.132
CCD	1.371	0.494	4.793	**0.035**	0.693	0.713	2.886	0.170

ICH: intracranial hemorrhage; NIHSS: national institutes of health stroke scale; ASPECTS: Alberta stroke program early CT score; CBF / CBV: cerebral blood flow / volume; OR: odds ratio. Note: A binary logistic regression analysis was performed for the indicated complications for the patient selection according to Figure 2. Bold p values indicate statistical significance.

Building on this, we could show that the mere presence of CCD in the acute phase has no impact on functional outcome in ischemic stroke patients. The original notion of diaschisis being a reversible condition, either in the form of CCD or transhemispheric diaschisis,[43] is not contradicted by our observations as significant clinical improvement was observed in patients with acute CCD. Animal studies of transhemispheric diaschisis have proven reversibility of the acute flow alterations in the subacute phase of stroke. However, as WB-CTP is not established as a method of follow-up imaging due to reasons of radiation hygiene, our study cannot validate the reversibility of CCD in these clinically improved patients. Still, our results support previous reports suggesting that rather chronic than acute CCD is associated with irrevocable brain degeneration[17,28] and impaired neurologic function.[25] The differences, however, might also be partially influenced due to other imaging techniques and inclusion criteria.

In contrast to functional patient outcome and final infarction volume, the occurrence of parenchymal hematoma was associated with the presence of CCD. As opposed to hemorrhagic infarction, parenchymal hematoma (in particular type II) has been shown to impair patient outcomes.[39] Besides IV thrombolysis, risk factors for parenchymal hematoma development are early ischemic changes,[44] prior medication with anticoagulants,[45] severe leukoaraiosis,[46] decreased cerebral blood flow, and increased blood-brain barrier permeability.[47–52] However, we only observed a non-significant trend for IV thrombolysis treatment towards parenchymal hematoma development. This might be explained by the sample size, the inclusion criteria, and/or by clinical patient selection for IVT. From a pathophysiologic point of view, we could not establish an explanation linking CCD with parenchymal hematoma development. Neither size nor severity of the acute ischemic injury had an independent influence in our study population. Yet, after further clinical validation, CCD could potentially serve as a quickly identifiable prognostic parameter in routine clinical stroke work-up.

Similar to the impact of CCD on patient outcome measures, factors influencing occurrence and severity of CCD are controversial. In line with previous studies,[9,11,28,29] we found a significant positive association between the size of the supratentorial perfusion deficit and CCD occurrence. It is important to note, however, that the final infarction volume was not associated with CCD. This result fits well with the missing association between CCD and functional outcome and with the proposed notion that acute CCD is a temporary and potentially reversible condition.

Our data must be interpreted in the context of the study design. As a first limitation, the most commonly used functional outcome measure, mRS at 90 days, was not available for all patients. Due to missing associations of CCD with other outcome measures that were fully available to us (discharge mRS, final infarction volume), we however expect that our results can be confirmed in larger prospective study cohorts. Second, the study was conducted in a retrospective fashion which does not allow a sample size estimation and power analysis. We would, however, like to point out that the present study includes the largest number of patients that were examined in the immediate stroke situation, underscoring the clinical relevance of the results. Finally, CCD presence was assessed

qualitatively in a dichotomized fashion, reflecting current practice in the clinical routine. We cannot rule out that a quantitative approach would lead to different results.

In conclusion, our study suggests that the presence of CCD in the acute phase has no significant impact on functional outcome in patients with ischemic stroke. The association between acute CCD and occurrence of parenchymal hematoma, however, is a noteworthy finding that warrants further research.

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Declaration of conflicting interests

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Authors' contributions

Conceived and designed the experiments: WGK, WHS, KMT. Performed the experiments: WGK, WHS, LVB. Analyzed the data: WGK, CH, MPF, FS, WHS, LVB. Wrote the manuscript: WGK, WHS, MPF, FS, FD, AEO, FGM, LVB, MFR, BEW, KMT.

Supplementary material

Supplementary material for this paper can be found at http://journals.sagepub.com/doi/suppl/10.1177/0271678X16686594

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6.2 Veröffentlichung II: Differential Benefit of Collaterals for Stroke Patients Treated with Thrombolysis or Supportive Care: A Propensity Score Matched Analysis

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ORIGINAL ARTICLE

Differential Benefit of Collaterals for Stroke Patients Treated with Thrombolysis or Supportive Care

A Propensity Score Matched Analysis

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Abstract

Purpose Leptomeningeal collaterals can slow down infarction growth; however, despite good collaterals in the DAWN and DEFUSE 3 trials, outcomes were devastating if reperfusion was not attempted. The aim of this study was to compare the influence of collaterals on morphological and functional outcome in patients with acute middle cerebral artery (MCA) stroke undergoing intravenous thrombolysis (IVT) vs. supportive care (non-IVT).

Methods Out of 1639 consecutive patients examined with multiparametric computed tomography (CT) for suspected ischemic stroke, all patients with confirmed MCA stroke who did not undergo endovascular thrombectomy were selected. Propensity score matching (PSM) was used to match IVT and non-IVT treated patients for potential confounders including age, sex, National Institutes of Health Stroke Scale (NIHSS) score on admission, Alberta Stroke Program Early CT Score (ASPECTS), and occlusion site. Regression analysis after PSM was performed to identify independent associations.

Results After PSM, 90 IVT patients were matched with 90 non-IVT patients. In multivariable regression analysis, a high regional leptomeningeal collateral (rLMC) score was independently associated with lower final infarction volume (FIV) in the IVT group (b = –0.472, $p < 0.001$) but not in the non-IVT group (b = –0.116, $p = 0.327$). The trichotomized rLMC scores predicted functional outcome in IVT treated patients (adjusted odds ratio, aOR = 4.57, 95% confidence interval, CI, 1.03–20.32, $p = 0.046$) but showed no independent association with outcome in the non-IVT group (aOR = 0.69, 95% CI 0.07–6.80, $p = 0.753$).

Conclusion Good collaterals favored smaller FIV and good functional outcome in IVT treated patients but not in non-IVT treated patients. Good collateral flow may have limited prognostic value if IVT is not administered to attempt reperfusion

Keywords IVT · Ischemia · CBV · CT perfusion · Cerebral circulation

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00062-019-00815-y) contains supplementary material, which is available to authorized users.

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Introduction

Collateral blood supply plays an important role in the pathophysiology of acute ischemic stroke [1, 2]. The arterial collateralization consists of primary collaterals from the circle of Willis and secondary collaterals via leptomeningeal or ophthalmic arteries. Through primary collaterals, the blood supply to ischemic regions can be delivered immediately as these are pre-existing. Secondary leptomeningeal collaterals may need time to develop the required capacity even if they are anatomically present [1]. These collateral circuits help to maintain perfusion to ischemic regions [2, 3]. Studies have shown great variance in the extent of collaterals throughout stroke patients [1]. Also, the presence and extent of collaterals affect both the severity and time course of stroke [3, 4]. According to recent studies, collateral assessment can yield important information on the success of recanalization and reperfusion, hemorrhagic transformation and functional outcome after stroke [5–7]. Several studies have shown the benefit of good collateral status for patients treated with endovascular therapy (EVT) [5, 8] or intravenous thrombolysis (IVT) [6, 9–11]. Therefore, collaterals can be used for decision making on whether to attempt reperfusion [7].

While collaterals can maintain perfusion to the penumbral area [4, 12], this bridging mechanism may break down or become ineffective over time [13]. Recent trials that extended the time window for EVT, i.e. DAWN [14] and DEFUSE 3 [15], illustrated that even highly selected patients with excellent collaterals and small ischemic cores had very poor outcomes if reperfusion was not attempted; however, the importance of collaterals in patients receiving solely supportive care remains unclear. This study aimed to evaluate the benefit of collaterals for stroke patients treated with IVT compared to those receiving only supportive care (non-IVT).

Material and Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

This study was approved by the institutional review board of the LMU Munich and carried out according to the Declaration of Helsinki of 2013; the requirement for informed consent was waived. Subjects were selected from a prospectively acquired cohort of 1639 patients who had undergone multiparametric computed tomography (CT) including whole-brain CT perfusion (WB-CTP) for suspected stroke.

Inclusion criteria were:

1. Initial multiparametric stroke CT with sufficient quality of non-contrast CT (NCCT), CT angiography (CTA) and WB-CTP
2. Acute middle cerebral artery (MCA) ischemia with confirmed infarction during follow-up
3. No treatment with endovascular thrombectomy and
4. Complete availability of clinical and imaging parameters.

To reduce potential bias by confounding variables, propensity score matching (PSM) was performed. Details of PSM are described in the statistics section.

Image Analysis

Detailed methods on CT protocols are provided in the online-only Data Supplement.

The initial NCCT, CTA, and WB-CTP were independently evaluated by two readers, 1 board certified attending radiologist (K.M. Thierfelder) with over 12 years of experience in stroke imaging and one 5th year radiology resident (W.G. Kunz) with over 5 years of experience in stroke imaging.

Ischemic changes on NCCT were evaluated using the Alberta Stroke Program Early CT Score (ASPECTS) [16]. The extent of collateralization was scored using the regional leptomeningeal collateral score (rLMC score) by Menon et al. [17] on single-phase CTA. This score compares the arterial supply in ASPECTS regions M1–M6, the anterior cerebral artery region, basal ganglia and Sylvian sulcus, with the contralateral hemisphere (0 no arteries seen, 1 less prominent and 2 equal or more prominent than the contralateral hemisphere). The collaterals in the Sylvian sulcus are weighted double, yielding a final rLMC score that ranges from 0–20, with 0 indicating the worst possible collateral status. According to the study of Menon et al. [17], the rLMC score was trichotomized for outcome analysis. A score of 17–20 was defined as good, 11–16 as medium and 0–10 as poor collateral status. The final infarction volume (FIV) was determined using the segmentation algorithm previously described [18, 19]. Perfusion deficit and mismatch were evaluated using the ASPECT score for cerebral blood flow (CBF) and volume (CBV) maps [20–22].

Clinical Data

The severity of stroke symptoms on admission was rated using the National Institute of Health Stroke Scale (NIHSS) [23]. For functional outcome measurement, the modified Rankin scale (mRS) [24] scores on admission and on discharge after the stroke event were obtained. Furthermore,

the premorbid mRS score representing patient disability prior to the current stroke event was estimated by considering the medical history of the patient. Cardiovascular risk factors and time from symptom onset (TFSO) to initial CTP imaging were collated.

Treatment

Patients were treated according to the institutional stroke protocol. The IVT was administered using 0.9 mg/kg body weight i.v. alteplase (rt-PA), with a maximum dosage of 90 mg. The IVT treatment was not performed if there were contraindications for IVT or patients showed spontaneous recovery prior to treatment.

Statistical Analysis

The SPSS Statistics 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Normal distribution was evaluated by the Kolmogorow-Smirnow test. Normally distributed variables were compared using the independent samples t-test. For non-normally distributed data the χ^2-test or Fisher's exact test was applied for categorical and the Mann-Whitney U-test for continuous or ordinal data. Analysis of predictive factors was performed with multivariable linear regression analysis for morphological outcome. For the functional outcome analysis, binary logistic regression was used to calculate adjusted odds ratios (aOR) for outcome at discharge (mRS ≤ 2) and *P*-values lower than 0.05 were considered significant.

Propensity Score Matching

The PSM was performed to ensure an even distribution of possible confounders in the IVT and non-IVT group [25, 26]. The IBM SPSS Statistics 25.0 and R Essentials Plug-In for SPSS were used for calculations. Nearest neighbor matching with 1:1 matching and a caliper of 0.2 standard deviations was performed. Matching covariates were age, sex, NIHSS score on admission, ASPECTS and location of the dominant occlusion on CTA. After matching descriptive statistics of patient characteristics, these were analyzed again to confirm successful matching and even distribution of the aforementioned parameters. Interaction term analysis was performed to test for interactions between the rLMC score and treatment status.

Results

Patient Characteristics Before and After Propensity Score Matching

In the initial cohort of 1639 patients, a total of 279 patients with MCA stroke fulfilled the inclusion criteria. Of this population, 141 received IVT (IVT group) while 138 did not (non-IVT group). The PSM resulted in a final study population of 180 matched patients (90 IVT group, 90 non-IVT group). Excluded from functional outcome analysis were a further 20 patients with incomplete mRS data, 9 patients with premorbid mRS > 1, 7 patients with death due to other causes, 6 patients with a second stroke event and 10 patients with previous stroke, malignancy and dementia. A flow chart of patient selection is provided in Fig. 1.

Descriptive statistics prior to matching revealed significant differences between the IVT and the non-IVT group for age (71 years, interquartile range, IQR: 62–81 years vs. 75 years, IQR: 67–84 years; $p = 0.023$), time from symptom onset to initial CTP (135 mins, IQR: 101–202 mins vs. 168 mins, IQR: 119–296 mins; $p = 0.001$), admission NIHSS (6, IQR: 2–11, vs. 8, IQR: 4–12; $p = 0.016$), CBF-ASPECTS (5, IQR: 3–8 vs. 7, IQR: 3–9; $p = 0.005$), mismatch-ASPECTS (2, IQR: 0–3 vs. 1, IQR: 0–2; $p = 0.001$) and occlusion location ($p = 0.038$). To ensure an even distribution of possible confounders within both groups, PSM was performed. Known predictors of the outcome for the propensity score calculation were selected. These matching variables were age, sex, NCCT-ASPECTS, occlusion location and NIHSS on admission. After PSM, a total of 180 patients ($n = 90$ in each group) formed the matched sample for further analysis. There were no significant differences between the groups in age, sex, admission NIHSS, NCCT-ASPECTS, and occlusion location (all $p > 0.05$). The median rLMC score was 18 (IQR: 15–20) in the IVT group and 18 (IQR: 12–20) in the non-IVT group after PSM. Notably, there was a significantly higher number of space-occupying edemas in the non-IVT group after PSM. Hemorrhagic infarction and parenchymal hematoma showed no significant differences. A detailed table of subacute stroke complications is provided in the online-only data supplement. A detailed mRS plot stratified by collateral status and IVT treatment is also provided in the online-only data supplement. Detailed patient characteristics before and after PSM are shown in Table 1.

Association of Collaterals with Morphological Outcome

For morphological outcome analysis final infarction volume on follow-up imaging was assessed. All 90 patients from the IVT group and all 90 patients from the non-IVT

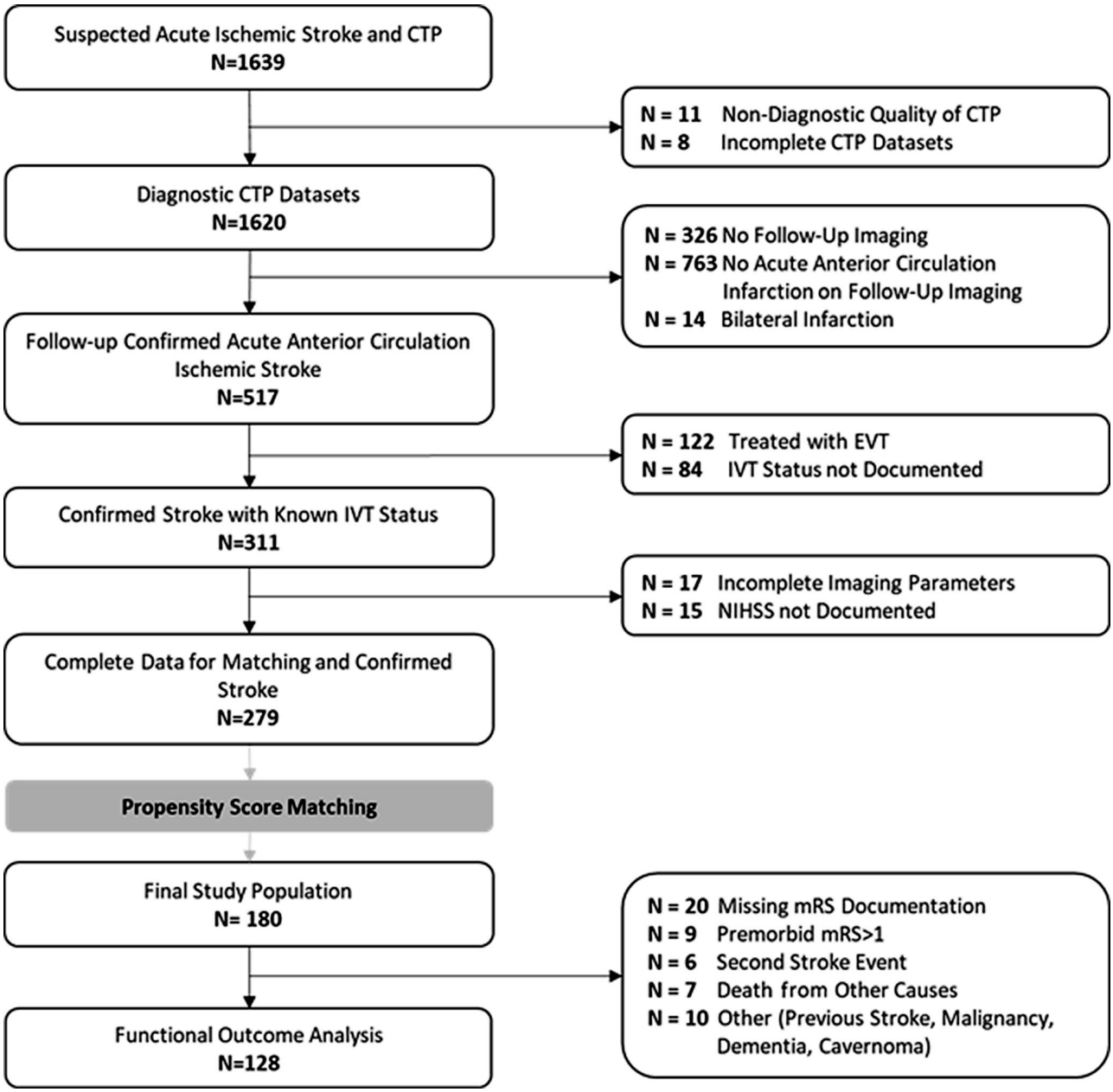

Fig. 1 Flow chart of patient selection. *CTP* computed tomography perfusion, *EVT* endovascular thrombectomy, *IVT* intravenous thrombolysis, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Rankin scale

group were included. Multivariable regression analysis adjusted for rLMC score, age, sex, admission NIHSS, ASPECTS, occlusion location and CBV-ASPECTS was performed to identify independent associations. A high rLMC score showed an independent association with a smaller FIV in the IVT group (standardized b = –0.472, $p < 0.001$). In contrast, the rLMC score did not show any association with FIV in the non-IVT group (standardized b = –0.116, $p = 0.327$). Higher CBV-ASPECTS was a strong predictor of low FIV in the non-IVT group (standardized b = –0.438, $p < 0.001$); however, no statistically significant interaction terms were observed between rLMC and IVT treatment status regarding the morphological outcome parameters. Detailed information of regression coefficients and *p*-values is presented in Table 2.

Association of Collaterals with Functional Outcome

For the analysis of functional outcome, 55 patients from the non-IVT and 73 from the IVT group were included.

Table 1 Patient characteristics of IVT and non-IVT groups before and after PSM

	Before PSM ($n=279$)					After PSM ($n=180$)				
	Non-IVT ($n=138$)		IVT ($n=141$)		*P*-value	Non-IVT ($n=90$)		IVT ($n=90$)		*P*-value
Patient Data										
Age (years)	71	(62–81)	75	(67–84)	*0.023**	71	(62–82)	72	(61–83)	0.802
Female sex	73	(52.9%)	69	(48.9%)	0.438	53	(58.9%)	49	(54.4%)	0.547
Time from Symptom Onset to initial CTP (mins)	168	(119–269)	135	(101–202)	*0.001**	158	(120–286)	137	(106–216)	0.121
NIHSS on Admission	6	(2–11)	8	(4–12)	*0.016**	7	(3–12)	6	(3–11)	0.597
Imaging Data										
NCCT-ASPECTS	9	(7–10)	9	(8–10)	0.639	9	(7–10)	9	(8–10)	0.872
rLMC Score	18	(13–20)	17	(14–20)	0.593	18	(12–20)	18	(15–20)	0.227
Occlusion Location										
No Occlusion	74	(53.6%)	51	(36.2%)	*0.038**	41	(45.6%)	40	(44.4%)	1.000
ICA/Carotid T	23	(16.7%)	28	(19.9%)		17	(18.9%)	18	(20.0%)	
M1 Segment of MCA	22	(15.9%)	38	(27.7%)		16	(17.8%)	16	(17.8%)	
M2 Segment of MCA	13	(9.4%)	19	(13.5%)		11	(12.2%)	11	(12.2%)	
M3 Segment of MCA	6	(4.3%)	5	(3.5%)		5	(5.6%)	5	(5.6%)	
Final Infarction Volume (ml)	52.9	(7.42)	51.5	(6.97)	0.504	50.3	(9.00)	43.2	(6.73)	0.904
CBF ASPECTS	7	(3–9)	5	(3–8)	*0.005**	6	(3–8)	6	(3–8)	0.708
CBV ASPECTS	9	(6–10)	8	(6–9)	0.123	9	(6–10)	8	(6–9)	0.798
Mismatch ASPECTS	1	(0–2)	2	(0–3)	*0.001**	1	(0–2)	2	(0–3)	0.345
Functional Data										
Premorbid mRS	0	(0–0)	0	(0–0)	0.804	0	(0–0)	0	(0–0)	0.403
Admission mRS	3	(2–4)	4	(3–4)	0.075	4	(3–4)	3	(2–4)	0.239
Discharge mRS	3	(1–4)	3	(1–4)	0.835	3	(1–4)	2	(1–4)	0.187
Cardiovascular Risk Factors										
Arterial Hypertension	106	(79.1%)	111	(80.4%)	0.785	72	(82.8%)	69	(77.5%)	0.385
Atrial Fibrillation	59	(44.0%)	62	(44.9%)	0.882	34	(39.1%)	33	(37.1%)	0.785
Smoking	41	(30.6%)	43	(31.4%)	0.888	23	(26.4%)	29	(33%)	0.346
Hypercholesterinemia	49	(36.6%)	61	(44.2%)	0.200	28	(32.2%)	37	(41.6%)	0.197
Diabetes	29	(21.6%)	33	(24.1%)	0.632	18	(20.7%)	20	(22.7%)	0.744

Values presented are counts (percentage) for categorical and median (interquartile range) or mean (standard error) for ordinal or continuous variables. Proportion analysis tests for categorical variables were performed using the χ^2-test. Nonparametric tests for non-normally distributed continuous or ordinal variables were performed using the Mann-Whitney U-test

NIHSS National Institutes of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early CT Score, *rLMC score* regional leptomeningeal collateral score, *ICA* internal carotid artery, *MCA* middle cerebral artery, *CBF* cerebral blood flow, *CBV* cerebral blood volume, *mRS* modified Rankin scale, *PSM* propensity score matching, *IVT* intravenous thrombolysis, *NCCT* non contrast computed tomography, *CTP* CT perfusion

*statistically significant

Good functional outcome (defined as discharge mRS ≤ 2) was achieved by 40.0% in the non-IVT and 54.8% in the IVT group ($p=0.097$). The trichotomized rLMC score was applied in binary regression analysis as prior studies identified the trichotomized [17] score as a good predictor of functional outcome. Using binary logistic regression analysis in the IVT and non-IVT subgroups, odds ratios adjusted for trichotomized rLMC score, age, sex, NIHSS on admission, ASPECTS, occlusion location and CBV-ASPECTS were obtained. Trichotomized rLMC scores were associated with a good outcome in the IVT group (aOR: 4.57, 95% CI 1.03–20.32, $p=0.046$), while it showed no significant association in the non-IVT group (aOR: 0.69, 95% CI 0.07–6.80, $p=0.753$); however, no statistically significant interaction terms were observed between rLMC and IVT treatment status regarding the functional outcome parameters. Detailed data are shown in Table 3.

Discussion

This study investigated the prognostic value of the collateral circulation in patients who underwent IVT as compared to those only receiving supportive care. Using PSM and re-

Table 2 Predictors of morphological outcome

	Final infarction volume			
	No IVT ($n=90$)		IVT ($n=90$)	
Independent variables	β	*P*-value	β	*P*-value
Age	–0.061	0.412	0.003	0.972
Sex	0.003	0.963	0.046	0.577
NIHSS on admission	0.315	*<0.001**	0.321	*<0.001**
NCCT-ASPECTS	–0.051	0.624	–0.016	0.861
Most proximal site of occlusion	–0.009	0.906	–0.047	0.55
rLMC score	–0.116	0.327	–0.472	*<0.001**
CBV-ASPECTS	–0.438	*<0.001**	–0.118	0.241

A multivariable linear regression analysis was performed for the indicated morphologic outcome parameters for the two subgroups of each 90 patients
NIHSS National Institutes of Health Stroke Scale, *NCCT* non-contrast enhanced CT, *ASPECTS* Alberta Stroke Program Early CT Score, *rLMC score* regional leptomeningeal collateral score, *CBV* cerebral blood volume
*statistically significant

Table 3 Predictors of functional outcome

	Good functional outcome at discharge (mRS ≤ 2)			
	No IVT ($n=55$)		IVT ($n=73$)	
Independent variables	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
Age	0.95 (0.90–1.00)	*0.050**	0.97 (0.93–1.02)	0.299
Sex	1.14 (0.26–4.95)	0.863	1.55 (0.35–6.77)	0.561
NIHSS on admission	0.78 (0.64–0.95)	*0.012**	0.76 (0.64–0.91)	*0.003**
NCCT-ASPECTS	2.23 (0.96–5.18)	0.063	1.09 (0.66–1.82)	0.734
Most proximal site of occlusion	1.24 (0.67–2.30)	0.491	1.88 (0.93–3.79)	0.08
Trichotomized rLMC score	0.71 (0.07–6.96)	0.767	4.57 (1.03–20.32)	*0.046**
CBV-ASPECTS	0.86 (0.61–1.22)	0.402	1.15 (0.79–1.68)	0.468

A binary logistic regression analysis was performed for the indicated clinical outcome parameters for the eligible patients
mRS modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *NCCT* non-contrast enhanced CT, *ASPECTS* Alberta Stroke Program Early CT Score, *rLMC score* regional leptomeningeal collateral score, *CBV* cerebral blood volume, *aOR* adjusted odds ratio
*statistically significant

gression analysis, good collaterals were identified as an independent predictor of a smaller final infarction volume and a better functional outcome if IVT is administered. In contrast, collaterals did not predict morphological or functional outcome in the supportive care group.

The presence and extent of collateralization both play an important role in sustaining perfusion to the penumbral regions in acute ischemic stroke. Good collateral blood supply can mitigate the neurological symptoms in patients with proximal artery occlusion [3]. From a mechanistic point of view, leptomeningeal collaterals are linked to the treatment effectiveness of IVT as they enable exposure of the proximal and distal parts of the clot to the thrombolytic drug [1, 27], and provide a route to wash out the dissolved thrombotic material [27, 28], thus, explaining the prognostic value of good collateral status in the IVT group as observed in this study; however, there are patients that show further deterioration in the course of an ischemic stroke, which can be explained by collateral failure [3, 13, 29]. Established concepts of collateral failure involve either the drop-out of auxiliary blood flow routes or the insufficiency of the collaterals to sustain the required blood flow to the ischemic area [3]. An important additional pathophysiological explanation for collateral failure is the inevitable resulting increase in microvascular resistance in the course of brain tissue hypoperfusion [30]. Regarding the natural history, this could explain why patients with good collaterals may still develop larger infarct volumes due to collateral failure at some point if treatment is not attempted. This infarction growth, however, might stop after successful reperfusion therapy by means of IVT and/or EVT. It has been shown by Tan et al. that good collaterals favor a better outcome in patients with large volume infarcts and may help select patients for IVT [31]. There are several more studies in the context of IVT, emphasizing the predictive value of collaterals for functional outcome after treatment [6, 9–11]. The present results in the IVT group reflect these findings, showing that collaterals are an important prognostic param-

eter if treatment is attempted; however, there is a lack of data in the supportive care context.

In the non-IVT group, collateral status was not suitable for the prediction of functional outcome. Therefore, patients with good collaterals without any attempts of reperfusion might also suffer worse functional outcome. This phenomenon could be attributed to collateral failure as discussed. Consequently, patients should not be excluded from reperfusion strategies due to good collateral circulation. In the current context of broadening EVT indications, these findings may translate into a rationale for the use of reperfusion in patients with EVT-treatable occlusion who suffer only minor deficits with low initial NIHSS as a result of good collateral circulation.

An important study on the outcome of patients not receiving stroke treatment by Lima et al. identified age, NIHSS and collateral grading as independent predictors of good outcome [32]. In accordance with this study, in the present study it was observed that NIHSS predicted functional outcome in non-IVT treated patients but could not identify collaterals as an independent predictor in this patient population; however, the statistical analysis by Lima et al. could not adjust for CTP parameters as these were not available, potentially explaining the different observations. For the morphological outcome of non-IVT treated patients, the ischemic core on CTP may have more prognostic value than the collateral grading as observed in the present study.

There are limitations to this study that need to be taken into consideration when analyzing the results. First, this is a single-center study with a limited number of patients. Second, the study was designed in a retrospective fashion. Therefore, possible confounders and selection bias may be present. Creating the final study population with PSM aimed to rule out these biases and minimize errors. The PSM is a frequently used statistical method to generate a matched control group to a known treatment group [26]. Thereby, it can help to reduce potential bias [25] as it simulates the randomization process [33]. It was further shown that regression analysis can help to minimize small residual imbalances after matching and is favorably combined with matching [34]. The study used PSM to create two comparable groups out of the initial observational study cohort. Matching parameters were important clinical and imaging parameters that have been identified as predictors of outcome: age [35] and sex [36], admission NIHSS [35, 37], ASPECTS [16] and occlusion location [38–40]; however, no statistically significant interaction terms were observed between rLMC and IVT treatment status regarding the morphological and functional outcome parameters, which needs to be acknowledged when interpreting the results. A detailed analysis including interaction terms before and after PSM is provided in the online-only data supplement. Third, all patients receiving EVT were excluded as the aim was to analyze the differences between IVT and supportive care specifically, thereby largely excluding patients with proximal large vessel occlusions from the study cohort. Fourth, outcomes at 90 days after the stroke event were not available in a sufficient number of patients to enable statistical analysis. Fifth, data on recanalization after IVT were not available in the study cohort. Repeated non-invasive angiography was not performed as there was no clinical indication according to contemporary guidelines; however, it is acknowledged that recanalization status is an important variable in both groups that remains unknown in this study.

In conclusion, good collateral blood supply contains limited prognostic information for stroke patients ineligible for EVT in whom reperfusion with IVT is not attempted. The differential benefit of collaterals in the context of IVT and supportive care may reflect the pathophysiological observations made in the recent late window EVT trials [14, 15], in which the control groups still suffered poor outcomes despite being included based on very favorable imaging profiles. The findings therefore underline the importance of IVT especially in patients with good collateral circulation.

Author Contributions Conceived and designed the experiments: F. Schuler, W.G. Kunz, K.M. Thierfelder. Performed the experiments: F. Schuler, L.T. Rotkopf, M.P. Fabritius, K.M. Thierfelder, W.G. Kunz. Analyzed the data: F. Schuler, L.T. Rotkopf, W.G. Kunz, D. Apel. Wrote the manuscript: F. Schuler, L.T. Rotkopf, D. Apel, M.P. Fabritius, S. Tiedt, F.A. Wollenweber, L. Kellert, F. Dorn, T. Liebig, K.M. Thierfelder, W.G. Kunz.

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Conflict of interest F. Schuler, L.T. Rotkopf, D. Apel, M.P. Fabritius, S. Tiedt, F.A. Wollenweber, L. Kellert, F. Dorn, T. Liebig, K.M. Thierfelder and W.G. Kunz declare that they have no competing interests.

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