UNIVERSITÉ DE LORRAINE BioSE

ECOLE DOCTORALE BioSE
BIOLOGIE, SANTÉ et son ENVIRONNEMENT
ED 266

Ecole Doctorale BioSE (Biologie-Santé -Environnement)

Thèse

Présentée et soutenue publiquement pour l'obtention du titre de

DOCTEUR DE l'UNIVERSITE DE LORRAINE

Mention : « Sciences de la Vie et de la Santé »

par Arturo CONSOLI

La collatéralité et les anastomoses leptoméningées dans les accidents vasculaires cérébraux – Collateral circulation and leptomeningeal anastomoses in acute ischemic stroke

6 Décembre 2022

Membres du jury:

Rapporteurs :	**Pr. S. ALAMOWITCH**	**MD, Paris Sorbonne Université**
	Pr. T. TOURDIAS	**MD, PhD, Université de Bordeaux**
Examinateurs :	**Pr. C. BOUTET**	**MD, PhD, Université de Saint-Etienne**
	Dr. E. KERRIEN	**CR, PhD, Université de Lorraine**
Président du Jury :	**Pr. A. ROUCHAUD**	**MD, PhD, Université de Limoges**
	Dr. B. CHEN	**PhD, CHRU de Nancy, co-directrice de thèse**
	Pr. S. BRACARD	**MD, PhD, Université de Lorraine, directeur de thèse**

Laboratoire d'**I**magerie **A**daptative **D**iagnostique et **I**nterventionnelle – INSERM U1254

Bâtiment Recherche, CHRU de Nancy Brabois, Rue du Morvan, 54511 VANDOEUVRE-LES-NANCY

Acknowledgments

To Prof. Serge Bracard, for his continuous support and his clear supervision. He is an exemple of peaceful force that will guide me through the next steps of my career.

To Bailiang Chen, for her kind and rigorous co-direction. Her outstanding support represented the critical base to translate physiopathology into a different language.

To Prof. Jacques Felblinger and the IADI CIC-IT laboratory members, they have warmly welcomed me during my PhD and provided an ideal environment for the development of a multidisciplinary project.

To Dr. Georges Rodesch, for having given me the huge chance to follow him during my endless educational pathway and for teaching me how to "protect myself from the sunlight".

To Oz, Federico, Silvia, Alessandro and all the members of our Diagnostic Neuroradiology Department for their continuous support, their friendship and their efforts that allowed me to complete this meaningful step.

To Foch Hospital, for having trusted me and supported in all the phases of my early career.

To Prof. Salvatore Mangiafico, my first "Maestro", for having let me move my first steps as an Interventional Neuroradiologist and for lovely teaching me the respect for the patients and the importance of sharing our knowledge.

To my parents, my safe harbor and a light to my path. I hope you can always be proud of me.

To my sisters Paola and Maria Cristina, the pearls that I will always protect as an oyster would do.

To Fabrizio and Giovanni, to Serena and Domenico, for always being a source of inspired and brotherly love and their presence a flame that will always burn.

To Ezio and Vilma, for your sense of family and warm heart.

To Cinzia, my beloved wife, my life. For your true love, patience and lovely care. The ink to write together the book of life.

INDEX

ABBREVIATIONS AND SYMBOLS (in alphabetical order)

AIS: Acute Ischemic Stroke

ASITN/SIR: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology

ASPECTS: Alberta Stroke Program Early CT Score

AVM: Arterio-Venous Malformation

CA: Contact Aspiration

CBV: Cerebral Blood Volume

CC: Collateral Circulation

CCS: Careggi Collateral Score

CIC-IT: Centre d'Investigation Clinique - Innovation Technologique

CoT: Combined Technique

CT: Computed Tomography

CVP: Collateral Venous Phase

DAVF: Dural Arterio-Venous Malformation

DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3

DICOM: Digital Imaging and Communications in Medicine

ECASS-III: European Cooperative Stroke Study

IADI: Imagerie Adaptative Diagnostique et Interventionnelle

ICA: Internal Carotid Artery

IFA: Image Feature Analysis

IVT: Intra-Venous Thrombolysis

LVO: Large Vessel Occlusion

MCA: Middle Cerebral Artery

MRI: Magnetic Resonance Imaging

MT: Mechanical Thrombectomy

mTICI: modified Thrombolysis in Cerebral Infarction

mRS: modified Rankin Scale

NIHSS: National Institute Health Stroke Scale

PWI: Perfusion-Weighted Imaging

RCT: Randomized Controlled Trial

ROI: Region of interest

SAH: Sub-Arachnoid Hemorrhage

SR: Stent-like retrievers

TOI: Time of Interest

TTP: Time-to-peak

MEP: Maximum Enhancement Projection

MTT: Mean Transit Time

LIST OF TABLES AND FIGURES

RESUME DE LA THESE EN FRANÇAIS

Introduction

Les Accidents Vasculaires Cérébraux ischémiques (AVCi) représentent une pathologie grave, potentiellement mortelle causée par l'occlusion d'une artère cérébrale. La lésion ischémique déterminée par l'occlusion artérielle peut évoluer vers la nécrose du tissu cérébral si le flux sanguin n'est pas rapidement rétabli. Les AVCi se caractérisent par des taux élevés de mortalité et de morbidité et l'objectif de la prise en charge de cette maladie dans un contexte aigu est basé sur un diagnostic rapide et un choix approprié de traitement.

Les nouvelles preuves apportées par les récents essais contrôlés randomisés et publiés en 2015 ont permis le développement et la diffusion généralisée de la thrombectomie mécanique (TM), une procédure Malgré les excellents résultats obtenus depuis l'introduction de la MT en termes d'augmentation constante du taux de recanalisation des artères obstruées, le taux de bons résultats cliniques n'a pas suivi la même évolution.

Tous les patients traités par MT ne tirent pas bénéfice de ce type de procédure, et on a évoqué pour eux le concept de « reperfusions futiles ». L'hypothèse physiopathologique sous-jacente à ce phénomène semble s'appuyer sur la circulation collatérale (CC), un système d'anastomoses entre les artères léptoméningées corticales du cerveau qui pourrait alimenter le territoire d'une artère occluse par un flux rétrograde au travers de ces anastomoses.

Une attention croissante est accordée à la CC dans la littérature, bien que les informations sur son hémodynamique et la tolérance à l'évolution de l'ischémie restent encore très peu connues.

Objectifs de la thèse

L'objectif de cette thèse de sciences est d'analyser le rôle de la CC selon trois paramètres:

1. L'analyse de l'implication clinique de la CC en tant que facteur pronostique pour les patients présentant un AVCi;
2. Une analyse critique des images artériographiques afin d'évaluer une corrélation possible avec les événements physiopathologiques des AVCi;
3. Le développement d'un algorithme de post-traitement dédié aux images d'artériographie en 2D.

La thèse de sciences est constituée de trois sections différentes:

- Section 1: INTRODUCTION

Un chapitre introductif (chapitre 1) donnant un résumé du diagnostic, du traitement possible et les défis cliniques des AVCi. Cette partie introductive servira également à familiariser le lecteur avec le concept et la définition de la CC et son rôle dans les AVCi. Toutes ces notions sont développées plus en détail dans les sections suivantes;

- Section 2: RÉSULTATS PRÉLIMINAIRES

Ce deuxième chapitre (Chapitre 2) reprend les résultats préliminaires obtenus lors de mes expériences scientifiques antérieures dans le domaine de la CC au cours de mon programme de résidence et pendant le Master 2.

- Section 3 : ANALYSE DES PARAMETRES D'EVALUATION DES OBJECTIFS

Trois chapitres distincts (chapitres 3 à 5) sont consacrés au développement des trois paramètres d'évaluation susmentionnés de cette thèse.

Le chapitre 3 est focalisé sur l'impact clinique de la CC en tant que facteur pronostique dans l'AVCi. Cet aspect a été analysé dans l'article: *UNfavorable CLinical Outcome in patients with good collateral Scores: the UNCLOSE study. Consoli A, Pileggi M, Hasan A T M, Venier A, Sgreccia A, Pizzuto S, Coskun O, Di Maria F, Scarcia L, Lapergue B, Rodesch G, Bracard S, Chen B*. Le papier a été soumis au *Journal of Neuroradiology*.

Le chapitre 4 est axé sur l'analyse critique de la CC selon les caractéristiques artériographiques décrites dans l'article: *Angiographic collateral venous phase: a novel landmark for leptomeningeal collaterals evaluation in acute ischemic stroke. Consoli A, Pizzuto S, Sgreccia A, Di Maria F, Coskun O, Rodesch G, Lapergue B, Felblinger J, Chen B, Bracard S*. L'article a été publié dans le *Journal of NeuroInterventional Surgery (JNIS)*.

Le dernier chapitre est consacré au développement d'un algorithme de post-traitement spécifique pour l'évaluation de la CC directement sur des artériographies 2D. Le flux de travail technique et l'ébauche de la demande de brevet seront présentés dans ce chapitre.

Chapitre 1 : INTRODUCTION

Les AVCi représentent environ 80 % des AVC à la phase aiguë, tandis que les AVC hémorragiques représentent environ 20 % des cas. En France, les AVCi sont considérés comme la première cause de handicap dans la population adulte, la deuxième cause de démence et troisième cause de mortalité (*Haute Autorité de Santé, 2009*). Chaque année, environ 150 000 nouveaux AVCi sont signalés avec un taux de mortalité d'environ 15 à 20% au cours du premier mois après l'événement ischémique et environ 50% au cours de la première année (*Fery-Lemonnier E., 2009; Chevreul K, et al. 2013*). Le coût annuel de la gestion des AVCi avait été estimé à 8,9 milliards € en 2007, ce qui correspondait à aux 3 % du budget annuel du système de santé (*Chevreul K, et al. 2013*).

Actuellement, deux stratégies thérapeutiques principales sont disponibles pour le traitement de l'AIS: la thrombolyse intraveineuse (IVT) et la thrombectomie mécanique (MT). L'objectif de la MT est d'obtenir la recanalisation de l'artère obstruée de manière rapide, sûre et complète. Le nombre de procédures de MT suit une croissance constante dans le monde entier et en France environ 7500 procédures/année sont effectuées.

En revanche, certains sous-groupes de patients ne semblent pas bénéficier de la MT, ce qui détermine la condition d'un succès technique (la recanalisation de l'artère occluse) sans atteindre un résultat clinique favorable. Cette condition a été décrite dans la littérature comme une « recanalisation futile ». À l'heure actuelle, le taux de recanalisation futile se situerait entre 45 et 55 % (*Goyal M, 2016; van Horn N et coll., 2021*). Une possible explication physiopathologique de ce phénomène pourrait être recherchée dans le rôle de la CC.

La CC pourrait être définie comme un apport vasculaire rétrograde de la circulation cérébrale dans un territoire qui ne peut pas être vascularisé en raison de l'occlusion de l'artère qui perfuse normalement des zones cérébrales définies. La CC se développe grâce à des anastomoses préexistantes entre les artères corticales des territoires voisins.

Il est possible de soutenir que la CC intervient entre une macro-circulation, c'est-à-dire la circulation corticale cérébrale (les artères corticales et piales et les artérioles pénétrantes) et une microcirculation, conçue comme le réseau cortical des capillaires qui est responsable de l'autorégulation. En effet, certains auteurs ont interprété la CC comme un « modulateur » pour la réponse vasculaire d'autorégulation et pour certains phénomènes hémodynamiques spécifiques tels que le couplage neurovasculaire *(Vasquez HE et al., 2021)*.

La compréhension de l'hémodynamique des artères corticales du cerveau est encore limitée. Les valeurs de pression et la mesure du flux sanguin dans cette région découlent toujours des mesures

effectuées au cours des interventions microchirurgicales après craniotomie et qui ont été réalisées à l'aide de microsondes dans patients sans occlusion vasculaires (*Carter PL et coll., 1978; Bederson et coll., 1995*).

Chapitre 2 : RESULTATS PRELIMINAIRES

Le Chapitre 2 résume les résultats préliminaires obtenus lors d'une étude antérieure cordonnées par le Doctorant et centrée sur la corrélation entre la classification artériographique de la CC et les images obtenues par scanner de perfusion, montrant une corrélation significative entre le degré de CC et l'extension de la lésion ischémique, notamment le *core* ischémique, observé sur le scanner de perfusion.
Les conclusions de cette étude, l'étude CAPRI, publiée dans le *Journal of NeuroInterventional Surgery*, étaient en faveur d'une corrélation entre les deux méthodes d'imagerie. Ce travail a permis d'avancer dans la compréhension physiopathologique des AVCi en montrant l'importance de l'évaluation de la CC.

Une autre partie de ce chapitre décrit les résultats d'une étude préliminaire effectuée pendant le Master2 au sein du même laboratoire. L'objectif était d'analyser le type d'acquisition artériographique à utiliser pour la construction d'un algorithme de caractérisation de la CC en utilisant directement les images artériographiques afin de permettre une évaluation en temps réel. Un protocole « standard » (à 2 images/seconde) et un protocole « expérimental » (à 6 images/seconde) ont été comparés. Les deux protocoles d'acquisition sont disponibles et installées dans toutes les machines d'artériographie, mais seulement le protocole standard est utilisé dans le cadre des procédures de TM. Les résultats de cette étude ont permis de conclure qu'un protocole d'acquisition à 6 images/seconde est le plus adapté pour analyser la CC en raison de la quantité de données obtenus qui permettent d'analyser de manière plus spécifique la CC.
Ces travaux préliminaires ont permis de créer le substrat pour le développement technique de l'algorithme de caractérisation.

Chapitre 3: ANALYSE DE L'IMPACT CLINIQUE DE LA CIRCULATION COLLATERALE

Le rôle de la CC dans la détermination des résultats cliniques favorables a été largement décrit dans la littérature. Plusieurs articles ont montré comment la présence des vaisseaux collatéraux est asso-

ciée à des résultats cliniques favorables après traitement endovasculaire (*Bang OY et al., 2008, Bang OY et al., 2011, Ribo M et al., 2011, Liebeskind et al., 2014, Consoli et al., 2016, Mangiafico S et al., 2014, Liggins JT et al., 2015, Seners P et al., 2019*, *Tong et al., 2018, Leng X et al., 2015*). Compte tenu de l'ensemble de la population présentant un AVCi, il a été démontré qu'environ 45 à 55% des patients traité avec succès par TM n'atteindra pas une indépendance fonctionnelle (*Goyal et al., 2016, van Horn et al., 2021*).

Les patients ayant un bon profil collatéral sont généralement considérés comme les candidats les plus favorables pour la TM, car ceux-ci sont associés à des conditions cliniques moins graves et avec lésions ischémiques plus limitées (*Consoli et al., 2016*). Cependant, aussi les patients avec de bons collatéraux peuvent ne pas bénéficier de la TM, malgré un tableau de perfusion cérébrale et clinique favorable, bien qu'une analyse des facteurs qui déterminent un mauvais résultat clinique dans ce sous-groupe spécifique de patients n'ait pas déjà été effectuée.

Par conséquent, ce chapitre était axé sur l'analyse de l'impact clinique de la CC en tant que facteur pronostique d'un résultat clinique dans les AVCi traités par TM. En particulier, l'objectif était d'évaluer quels facteurs peuvent être associés à des résultats cliniques défavorables chez les patients présentant un bon profil collatéral. Cette question de recherche a été abordée dans l'étude UNCLOSE (*UNfavorable CLinical Outcomes in patients with good collateral Scores study*), une étude rétrospective d'une cohorte de patients avec une bonne CC, soumise dans le *Journal of Neuroradiology*.

Les résultats de l'étude UNCLOSE ont montré que même les patients ayant de bons collatéraux peuvent ne pas atteindre un résultat clinique favorable en termes, indépendamment de la technique endovasculaire ou du type de anesthésie utilisée. Les résultats globaux étaient partiellement similaires à ceux rapportés dans la littérature et pour les populations de patients avec une CC insuffisante. En effet, il s'agissait de l'un des premiers articles portant sur cette cohorte spécifique de patients avec une bonne CC.

Néanmoins, nous avons pu observer de mauvais résultats cliniques (mRS3-6) chez 47% des patients présentant une bonne CC évaluée à l'aide du score ASITN/SIR. Le taux de mortalité était de 13,6 %. Le rôle de la thrombolyse IV en tant que facteur « protecteur » est conforme aux résultats actuels rapportés par l'étude SWIFT DIRECT, récemment publiée dans le Lancet, qui a montré que l'association IVT + MT était associée à un meilleur résultat clinique que la TM seule (*Fischer U et al., 2022*).

Ces données sont particulièrement intéressantes si l'on considère que cette cohorte est considérée comme la plus susceptible d'atteindre une indépendance fonctionnelle après TM et que les résultats cliniques étaient indépendants du type de technique endovasculaire ou du type d'anesthésie utilisée.

Ces résultats pourraient soulever certaines questions concernant la manière d'évaluer la CC et la valeur pronostique de cette dernière chez les patients présentant un AVCi.

Chapitre 4 : ANALYSE CRITIQUE D'EVALUATION DE LA CIRCULATION COLLATERALE SUR LES IMAGES D'ARTERIOGRAPHIE CEREBRALE

Le rôle principal de la CC est de moduler l'évolution du processus ischémique, en fournissant une sorte de « réserve hémodynamique » en cas d'occlusion artérielle. Cependant, les patients avec de bons vaisseaux collatéraux peuvent également être associés à des résultats défavorables ou, au moins, ne pas atteindre une indépendance fonctionnelle.
Par conséquent, même les patients qui sont considérés comme les meilleurs candidats à la TM selon les critères actuels (échelle ASITN/SIR) peuvent ne pas bénéficier du traitement endovasculaire et en particulier ceux qui ont un âge plus avancé, sans administration de thrombolyse IV et traités avec des temps de procédure prolongés. La classification la plus utilisée en littérature est celle de l'ASITN/SIR qui décrit une échelle de 5 grades pour l'analyse de la CC (tableau 3), sur la base d'une évaluation qualitative de cette circulation. L'évaluation quantitative associée reste très chronophage et le degré de reproductibilité est très limité (*Ben Hassen W et al., 2019).*

Afin d'évaluer l'efficacité de la CC, nous avons proposé l'analyse de la CC sur la base du concept de la perméabilité du côté veineux des vaisseaux collatéraux. Selon cette théorie, l'efficacité de la CC serait également liée à l'efficacité des veinules de la garantie circulation effectuant plusieurs tâches, telles que le dégagement des emboles en aval, le maintien du flux sanguin et effet préventif sur l'adhésion plaquettaire *(Tong et al., 2018).*

Les résultats de l'étude UNCLOSE avaient montré comme la modalité d'évaluation actuelle de la CC par artériographie, en utilisant les outils actuels, pourrait ne pas être adaptée compte tenu de ce nouveau paradigme qui met en évidence le rôle des veines et des venules de la CC dans la physiopathologie des AVCi.
L'analyse du sous-groupe de patients avec de bonnes collatérales et des résultats défavorables et la subjectivité de la l'évaluation de la CC soulèvent certains points de débat. En particulier: une CC évaluée comme une bonne circulation collatérale selon cette échelle est-elle également efficace? Cette question de recherche représentait l'objectif de l'article « *The angiographic collateral venous*

phase: are good collaterals always effective? » soumis dans le *Journal of NeuroInterventional Surgery*.

Cette étude rétrospective réalisée sur une population de 200 patients a permis d'analyser un paramètre pas encore évalué dans la littérature : la phase veineuse de la CC évaluée sur les images artériographiques. L'hypothèse de l'étude était centrée sur l'impact clinique de la visualisation des structures veineuses sous-corticales dans la région de la circulation collatérale. La présence de cette phase veineuse représenterait le signe indirect de la fonctionnalité de la CC, ce qui pourrait permettre de différencier la CC non seulement par rapport à son extension, mais surtout par rapport à la capacité de maintenir un flux fonctionnel dans les vaisseaux collatéraux.

L'étude a montré que l'analyse de la phase veineuse des collatéraux semble affiner l'évaluation de la CC. Bien que l'analyse basée sur l'échelle ASITN/SIR et l'analyse basée sur CVP aient montré des résultats globalement similaires et en ligne avec la littérature médicale (*Anadani et al. 2022, Mangiafico et al. 2014, Liebeskind et coll., 2022*), il a été possible d'observer une association bien plus significative entre la présence de la phase veineuse collatérale (CVP+) et le résultat clinique favorable (mRS à 3 mois) ainsi qu'en termes de taux de transformation hémorragique et de mortalité en comparaison avec l'évaluation effectuée par l'échelle ASITN/SIR. De plus, l'analyse composite qui correspondait à l'évaluation combinée de la CC par l'échelle ASITN/SIR et la présence/absence de la phase veineuse collatérale ont fourni des résultats solides en termes d'association avec des résultats cliniques favorables (OR: 6.56, CI95%[2,99-14,39]) et un risque plus faible de transformation hémorragique.

Une validation externe de ces résultats sera obligatoire afin de confirmer ces résultats, qui restent pour l'instant un outil générateur d'hypothèse.

Chapitre 5 : UN APPROCHE TECHNIQUE BASE SUR LA PHYSIOPATHOLOGIE : DÉVELOPPEMENT D'UN ALGORITHME POUR L'ÉVALUATION ANGIOGRAPHIQUE DE LA CIRCULATION COLLATÉRALE

Les résultats de l'analyse clinique et critique de la circulation collatérale, qui ont été discutés dans les chapitres précédents ont soulevé plusieurs questions sur l'évaluation de la circulation de la CC.
Il serait donc très avantageux que les images artériographiques prétraitement acquises in situ puissent être utilisées pour fournir des indications par rapport aux stratégies de traitement, telles que la sélection des patients pour la TM, le pronostic, les stratégies post-traitement, etc. Ce concept a

été abordé par le développement d'un algorithme dédié pour caractériser la CC basé sur les images artériographiques. Inspiré par et considéré comme une extension des travaux du Master2, dans ce chapitre sont décrites l'analyse des courbes temps-densité de la région de la CC extraites des données artériographiques. Différemment d'une étude basée exclusivement sur l'analyse d'une Région d'Intérêt (ROI), l'analyse en termes de pixels a été également appliquée. Une population de 108 patients présentant une occlusion du segment M1 de l'artère cérébrale moyenne (M1-MCA), éligibles à la procédure de TM et traités entre 2018 et 2021 à l'hôpital FOCH a été analysée. Tous les patients ont été imagés avec le protocole d'acquisition « expérimental » décrit précédemment (à 6 images/seconde).

Par la suite, un Core Lab Qualité dédié à analyser la qualité des images d'artériographie a été institué, qui comprenait deux neuroradiologues non impliqués dans les procédures. Le Core Lab Qualité a évalué la qualité des images et a indiqué l'éligibilité pour l'analyse. Les artefacts de mouvement ont représenté la principale raison d'exclusion et 19 patients ont donc été exclus.
Un groupe de variables a été évalué pour effectuer l'analyse critique des angiographies et le paramétrage de l'algorithme. Ces variables ont été résumées dans le plan analytique qui a été établi et nommé « Image Feature Analysis (IFA) ».
Afin de caractériser les angiographies, en particulier l'opacification liée au produit de contraste iodé, nous avons analysé de manière approfondie le comportement de la série artériographique, non seulement par régions (cérébrale, région collatérale, région du bassin versant, etc.) mais aussi par pixel afin de comprendre le comportement du contraste du tissu cérébral.

Analyse spatiale des régions observées

Les caractéristiques des images artériographiques ont été analysées sur la base d'une répartition dans 4 types de régions: la région cérébrale, région collatérale étendue, la région « critique » de territoire de dernier pré et la région collatérale pure, afin d'analyser les changements de trajectoire temporelle de l'opacification liée au produit de contraste des vaisseaux collatéraux dans le territoire cortical de l'artère cérébrale moyenne. Un premier processus de segmentation a été effectué manuellement à l'aide du logiciel ITK-SNAP.

Analyse semi-quantitative de la courbe de densité temporelle

L'évaluation de l'analyse de la courbe temps-densité basée sur la ROI a été effectuée en calculant les éléments des mappes paramétriques : *time-to-peak* (TTP), *mean transit time* (MTT), *maximum enhancement projection* (MEP). Alors que les interprétations étaient difficiles à réaliser sur les données TTP et MTT, les mappes MEP ont abouti à des résultats plus indicatifs pour donner la première

différentiation de la CC en « bonne » et « mauvaise » (nommées respectivement Group-gc « Good collaterals » et Group-pc « Poor collaterals »).

Complexité vasculaire dans la région collatérale

Afin de décrire quantitativement l'observation précédente et aussi prouver l'hypothèse qu'une bonne/mauvaise CC peut être différencié par le niveau de complexité vasculaire de la CC, nous avons utilisé la métrique appelée « dimension fractale », Ds, une méthode mathématique récente qui a été largement utilisée pour quantifier les vaisseaux rétiniens et les profils osseux trabéculaires en radiographie ou tomodensitométrie.

Concepts physiopathologiques intégrés

Pendant les travaux de la thèse, deux concepts physiopathologiques ont été développées et intégrés dans le développement de l'algorithme : la *désynchronisation* et les « *turning points* ».

Désynchronisation : la CC et la circulation cérébrale sont visualisés en différentes phases de l'artériographie et ceux-ci pourraient être considérés comme « désynchronisés ». Il pourrait être intuitif que plus le délai entre l'opacification de la normale circulation cérébrale antérograde et l'opacification de la CC est court et plus la vitesse de flux sera élevée dans la CC et donc dans le territoire ischémique. En fait, la perméabilité du côté veineux de la CC permet d'éviter une stase sanguine dans les vaisseaux collatéraux et de maintenir un flux sanguin stable dans le territoire ischémique et la perfusion de la microcirculation.

Turning points: La progression du produit de contraste dans la circulation cérébrale peut être clairement identifiée en trois phases différentes: artérielle, parenchymateuse/capillaire et veineuse. La transition entre deux phases consécutives peut être donc définie comme un tournant des deux phases (*turning point*). Les *turning points* aideraient à différencier la transition de la phase artérielle à la phase parenchymateuse et de la phase parenchymateuse à la phase veineuse. Ainsi, l'application des *turning points* aiderait à séparer et à différencier les phases artériographiques et pourrait fournir la base pour « quantifier » la désynchronisation entre la CC et la circulation cérébrale.

Le développement de l'algorithme permettra à terme une analyse en temps réel de la CC en particulier par rapport à son efficacité (présence de la phase veineuse de la CC) ainsi que par rapport à la vitesse de flux. Ce type d'évaluation permettra d'ajouter des éléments hémodynamiques utiles pour la compréhension physiopathologique des AVCi et pour la gestion des patients pour diminuer le risque de transformation hémorragique identifiant les patients avec une CC inefficace.

DEFINITION AND PRESENTATION OF THE THESIS

Acute ischemic stroke (AIS) represent a life-threatening condition caused by the occlusion of a cerebral artery and determining an ischemic lesion which can evolve toward the necrosis of the brain if the blood flow is not rapidly restored. AIS is characterized by high rates of mortality and morbidity and the goal of the management of this disease in an acute setting is based on a rapid diagnosis and a proper choice of treatment.

The new evidences brought by recent Randomized Controlled Trials (RCTs) in 2015 allowed the development and the widespread diffusion of Mechanical Thrombectomy (MT), a procedure performed though an endovascular approach to remove the clot occluding a cerebral artery.

Although the excellent results obtained with the introduction of MT in terms of a constant increase of the recanalization rate of the occluded arteries, the rate of clinical outcomes did not follow the same behavior. Therefore, it was clear that not all the patients treated by MT could benefit from this type of procedure, configuring the so-called “futile reperfusions”.

The physiopathological hypothesis underlying this phenomenon seems to rely on the collateral circulation (CC), a system of anastomoses between the cortical leptomeningeal arteries of the brain that could supply the territory of an occluded artery through a retrograde flow sustained by these anastomoses. Furthermore, an increasingly growing attention is being paid to CC in the literature, although very little is known about its hemodynamics.

The interest about CC raised up during the period of my Residency program in Radiology at the Careggi University Hospital in Florence (2010-2015), where I have started to build my scientific activity under the supervision of my first mentor, Dr Salvatore Mangiafico, the first interventional neuroradiologist in the world to perform a procedure of MT. During those years the knowledge about CC was very limited as well as it was the therapeutic management of AIS.

I have started to deeply study this subject, since I could clearly observe that this type of circulation played a major role in the prognosis and evolution of AIS. I have participated to the publication of two first papers about collaterals in 2013 (*Mangiafico S et al. 2013*) and 2014 (*Mangiafico S et al. 2014*). In the former paper we introduced a new grading system based on the Digital Subtraction Angiography (DSA) in order to provide a semi-quantitative and a qualitative assessment of CC th-

rough the Careggi Collateral Score (CCS), while in the latter we had observed that CC had a real impact on the clinical outcome of patients treated by MT.

From 2011 to 2015 I have coordinated a collaborative group which included the Careggi University Hospital (Florence), the Lescotte Hospital (Siena), the Sant'Agostino Estense Hospital (Modena), the University Hospital of Ferrara and the Karolinska Institute (Stockholm). This collaborative group focused on the comparison between the angiographic assessment of the CC through the Careggi Collateral Score and the perfusional aspect of the brain evaluated through the CT-Perfusion: the CAPRI Study (CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study). The retrospective analysis of our multicentric cohort led to the publication of the results of our paper on the *Journal of NeuroInterventional Surgery*, which is considered one of the most valuable journals in the domain of Interventional Neuroradiology (*Consoli A, et al. 2016*). The CAPRI Study represented also the final thesis of my Residency Program.

During the Master 2, in 2018, I had the chance to work on the CIC-IT/IADI Laboratory in Nancy, directed by Prof. Jacques Felblinger, under the close supervision of Dr Bailiang Chen and I have exposed my project to work on the imaging post-treatment in order to assess the qualitative aspect of CC directly on DSA. The preliminary work that I have conducted at the laboratory led to a basic version of an algorithm that segmented and evaluated the perfusional curves of the brain directly on the 2D angiograms that I had acquired using an experimental protocol at 6 frames/seconds.

This experience represented a milestone in the construction of the project of the PhD thesis. Indeed, considering the initial results that we had observed I felt very confident to continue this project following a more sophisticated roadmap. The team at CIC-IT/IADI Laboratory was very motivated as well. A strategy plan was built up in accordance with Prof. Serge Bracard, my PhD thesis Director, and Dr Mitchelle Bailiang Chen, my PhD thesis Co-director. Prof. Bracard and Dr Chen approved the subject of the PhD and the PhD thesis plan.

COVID-19 pandemic has overturned the entire world during her last two years and that has affected, at the very beginning, the workflow of my PhD project. However, we have rapidly thought about an alternative program and started weekly meetings with a remote work-based schedule. I had the possibility to continue the experimental and the clinical workflow at my institution, the Foch Hospital in Suresnes. I had the opportunity to work remotely with Dr Chen and we have mutually advanced in the development of a dedicated algorithm for the segmentation of the collateral vessels.

The final declared objective of this algorithm will be the assessment of the flow velocity within the CC.

Aim of the PhD thesis

The aim of my PhD Thesis was to investigate the role of the CC through:

1. The analysis of the clinical implication of the CC as a prognostic factor for patients with AIS
2. A critical analysis of the angiographic images in order to evaluate a possible correlation with the physiopathologic events of AIS
3. The development of a dedicated post-processing algorithm for 2D angiograms and the comparison with a pre-existing algorithm.

The PhD thesis will be constituted of three different sections:

- ***Section 1: INTRODUCTION***

An introductive chapter (Chapter 1) that will provide an overview about AIS, the diagnosis, the possible treatment and the clinical challenges. This introductive part will serve also to acquaint the reader with the concept and the definition of the CC and the role of CC in AIS. All these notions will be further developed in the following sections;

- ***Section 2: PREFATORY RESULTS***

A second chapter (Chapter 2) that resumes the Prefatory results obtained during my previous scientific experiences in the field of CC during my Residency Program and during the Master 2.

The following paper will be presented:

Consoli A, Andersson T, Holmberg A, Verganti L, Saletti A, Vallone S, Zini A, Cerase A, Romano D, Bracco S, Lorenzano S, Fainardi E, Mangiafico S; CAPRI Collaborative Group. CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study.

The paper was published in the Journal of Neurointerventional Surgery (JNIS) in 2016.

These preliminary results provided the basic concepts for the present work.

- ***Section 3: PhD ENDPOINTS***

Three separate chapters (Chapters 3-5) will focus on the three aforementioned endpoints of the PhD thesis.

Chapter 3 will be centered on the clinical relevance of the CC as a prognostic factor in AIS. This aspect was analyzed in the paper:

UNfavorable CLinical Outcome in patients with good collateral Scores: the UNCLOSE study. Consoli A, Pileggi M, Hasan A T M, Venier A, Sgreccia A, Pizzuto S, Coskun O, Di Maria F, Scarcia L, Lapergue B, Rodesch G, Bracard S, Chen B. Submitted to the *Journal of Neuroradiology*.

Chapter 4 will be focused on the critical analysis of the CC according to the angiographic characteristics that were described in the paper:

Angiographic collateral venous phase: a novel landmark for leptomeningeal collaterals evaluation in acute ischemic stroke. Consoli A, Pizzuto S, Sgreccia A, Di Maria F, Coskun O, Rodesch G, Lapergue B, Felblinger J, Chen B, Bracard S. Published in the *Journal of NeuroInterventional Surgery (JNIS)*.

The last Chapter will be dedicated to the development of a specific post-processing algorithm for the assessment of CC directly on 2D angiograms and to the use with a pre-existing algorithm. The technical workflow and the draft of the patent submission will be presented and discussed in this Chapter: **Algorithm of characterization of collateral circulation "REACH" – Real-time Assessment of Collateral circulation Hémodynamics in acute ischemic stroke)/*Algorithme de caractérisation de la circulation collatérale REACH (REal-time Assessment of Collateral circulation Hemodynamics in acute ischemic stroke)***

LIST OF PUBLICATIONS AND COMMUNICATIONS

1. Published papers - Peer-reviewed Journals

Consoli A, *Andersson T, Holmberg A, Verganti L, Saletti A, Vallone S, Zini A, Cerase A, Romano D, Bracco S, Lorenzano S, Fainardi E, Mangiafico S; CAPRI Collaborative Group. CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study. The paper was published in the Journal of Neurointerventional Surgery (JNIS) in 2016. J Neurointerv Surg. 2016 Dec;8(12):1211-1216. doi: 10.1136/neurintsurg-2015-012155. Epub 2016 Jan 22. PMID: 26801947.*

Consoli A, *Pizzuto S, Sgreccia A, Di Maria F, Coskun O, Rodesch G, Lapergue B, Felblinger J, Chen MB, Bracard S. Angiographic collateral venous phase: a novel landmark for leptomeningeal collaterals evaluation in acute ischemic stroke - The paper has been published in* the Journal of NeuroInterventional Surgery (JNIS) - 2023

2. Submitted papers - Peer-reviewed Journals

Consoli A, *Pileggi M, Hasan A T M, Venier A, Sgreccia A, Pizzuto S, Coskun O, Di Maria F, Scarcia L, Lapergue B, Rodesch G, Bracard S, Chen B. UNfavorable CLinical Outcomes in patients with good collateral Scores: the UNCLOSE study. – Submitted to the* Journal of Neuroradiology

3. Patent submission

Consoli A – CIC-IT IADI Laboratory. Algorithm of characterization of collateral circulation "ASCOT" (ASsessment of COllateral circulation hemodynamics in acute ischemic sTroke)/ ***Algorithme de caractérisation de la circulation collatérale "ASCOT" (ASsessment of COllateral circulation hemodynamics in acute ischemic sTroke)***

4. Communications

Invited Conference Speaker - Annual Camp Base Neurovascular course (CBNV, Rome) - "Angiographic and CT-Angiography assessment of collateral circulation" - September 2015

Invited Conference Speaker - National Congress Groupe de Réflexion sur la Cardiologie Interventionnelle (GRCI, Paris) - Prise en charge d'un AVC par un neuroradiologie interventionnel" - December 2017

Invited Conference Speaker - Annual National Congress of the Egyptian Stroke Conference (Cairo) - "Mechanical thrombectomy or thrombus aspiration? Insights from the ASTER and ASTER2 Trials" - December 2018

Invited Conference Speaker - SLICE Course (Nice) - "Clot imaging with DSA" - October 2019

Invited Conference Speaker – Italian Stroke Association (ISA) – "Lo studio dei circoli collaterali puo' sostituire le techniche di imaging per identificare la penombra nella selezione dei pazienti da sottoporre a trombectomia meccanica nelle finestre terapeutiche più lunghe?" – "Could the study of collateral circulation replace the imaging techniques to identify the penumbra to select patients for mechanical thrombectomy in late windows?" – Verona, December 2021

Invited Conference Speaker - Annual Camp Base Neurovascular course (CBNV, Rome) - "How to select patients for mechanical thrombectomy in acute ischemic stroke?" - September 2022

Section I - INTRODUCTION

1. INTRODUCTION

1.1. Acute stroke - Overall background

Acute stroke is considered as a life-threatening, emergency condition and it can be classified as: **acute ischemic stroke** (AIS) and **hemorrhagic stroke**.

The former is secondary to the occlusion of a cerebral artery, caused by a clot with different sources:

- **cardioembolic** (due to valvular or non-valvular cardiac diseases, atrial fibrillation, intra-cardiac tumors such as mixomas, valvular prosthetic implantation),
- **atheromatous** (secondary to the rupture of an instable atheromatous plaque located in the arterial wall of the carotid bifurcation/in the aortic arch or to the presence of an atheromatous plaque in a cerebral artery with an in-situ thrombosis),
- **infectious** (in case of bacterial/mycotic/viral endocarditis)
- **tumoral** (secondary to the hyper-coagulation induced by the biochemical reactions caused by the cancerous lesion)

Hemorrhagic strokes are mainly linked to the rupture of cerebral vascular structures (arteries, capillaries, veins) secondary to the aging or to the development of malformative diseases (aneurysms, ArterioVenous Malformations - AVMs, ArterioVenous cortical or dural fistulae - DAVF). According to the type of bleeding we can distinguish:

- typical intra-parenchymal hematomas, which are frequently observed in the elderly population, with associated hypertension and ongoing vascular aging phenomena (amyloid deposits, arteriosclerosis) in the so-called "typical" localizations such as the putamen, the lenticular nucleus, deep cerebral territories;

- atypical intra-parechnymal hematomas, which are often observed in younger patients without known vascular risk factors and which are located in atypical sites, such as (cerebral lobes, superficial territories, posterior cranial fossa, except for the pons). This subtype of hemorrhage stroke is frequently linked to vascular malformations (AVMs/DAFVs, dural or cortical fistulas);

- sub-arachnoid hemorrhages (SAH), which are mainly caused by the rupture of a cerebral aneurysm, whose fissuration determines a blood collection in the sub-arachnoid spaces, surrounding the

brain. Also other diseases can cause SAH, such as DAVFs and cortical AVMs, although this presentation is quite rare.

1.2 Epidemiology of Acute Ischemic stroke (AIS)

AIS represent about 80% of acute strokes, while hemorrhagic strokes account for about 20% of the cases. In France, AIS is considered the first cause of handicap in the adult population, the second cause of dementia and the third cause of mortality (*Haute Autorité de Santé, 2009*).

Every year about 150.000 new AIS are reported with a mortality rate of about 15-20% during the first month after the ischemic event and about 50% during the first year. This rate varies according to the type, localization and extension of the ischemic lesion. Among the survivors, the morbidity rate is about 50-75% because of the persistence of a neurological deficit ***(****Fery-Lemonnier E., 2009; Chevreul K, et al. 2013*).

1.3 Socio-financial burden of AIS

The annual cost of IAS management had been estimated in 8.9 billion € in 2007, which corresponded to the 3% of the annual budget of the Healthcare system (*Chevreul K, et al. 2013)*. The median cost of direct expenses every ischemic event is estimated at 16.686 €/patient during the first year (*Berkhemer OA et al., 2015*).

Furthermore, one should consider the indirect costs, such as those linked to the rehabilitation programs and the loss of productivity, which had been calculated respectively at 2.4 billions € and 255.9 millions € (*Berkhemer OA et al., 2015*).

1.4 Treatment of AIS patients

As aforementioned, AIS are secondary to the occlusion of a cerebral artery. However, the localization of the occlusion site allows to differentiate the lacunar AIS, which are caused by the occlusion of small arterial branches (perforating or isolated cortical branches) due to small clots, and the major strokes, which are due to the occlusion of large arteries of the Willis's polygon (the so-called "large vessel occlusions" - LVO). In general, lacunar strokes are associated with a more favorable prognosis and less neurological sequelae, while LVOs are mostly correlated with worse clinical outcomes and higher mortality rates (Goyal et al., 2016).

Most of the AIS is located in the carotid territory (anterior circulation, about 80-85% of the cases) and less than 20% are located in the vertebro-basilar territory (posterior circulation).

Clinical severity of AIS depends on the localization of the occluded artery and on the extension of the ischemic lesion in the involved territory. Indeed, the occlusions of an artery of the vertebro-basilar system are associated with higher mortality rates, although these are less frequent. AS far as the anterior circulation is concerned, the occlusions of the carotid siphon of the internal carotid artery (ICA) are associated with more severe clinical conditions as compared with the isolated occlusions of the middle cerebral artery (MCA).

Currently, two main therapeutic strategies are available for the treatment of AIS: the intravenous thrombolysis (IVT) and the mechanical thrombectomy (MT)

- IVT is an inhibitor of the plasminogen activator; therefore, this drug allows the clot lysis. The ECASS-III (*Hacke W et al., 2008*) had shown that patients could benefit of IVT administration (Alteplase) during the first 4.5 hours from the onset of the neurological symptoms, concluding that there was a significant improvement of clinical outcome without increasing the risk of a hemorrhagic transformation of the ischemic lesion. More recent trials, such as the DEFUSE-3 (*Albers et al., 2017*), showed the same clinical benefit without a temporal window limitation, but according to the perfusional status of the brain at the moment of the administration of the IVT. The effectiveness of IVT seems to be related to the clot length, since it has been shown that clots longer than 8 mm are significantly less responsive to IVT with Alteplase (*Campbell BC et al., 2016*). However, new lytic molecules, such as the Tenecteplase showed even better results in terms of effectiveness and safety profile, slightly increasing the recanalization rates (*Seners P et al., 2019*). Current guidelines of the AHA and the ESO (*Powers WJ et al., 2019; Berge E et al., 2019*) consider IVT as a first-line treatment for AIS in patients without contra-indications for IVT), in association with MT in case of LVOs.

- Mechanical Thrombectomy (MT) is a minimally invasive, endovascular procedure performed by Interventional neuroradiologists that allows the removal of the clot which occludes the cerebral artery. Different endovascular techniques are used to perform MT and in particular: the stent-like retriever (SR), the Contact Aspiration (CA) and the Combined Technique (CoT). All these techniques are performed through a femoral/radial/carotid arterial access (through the navigation of the aorta, the aortic arch and of vertebral or carotid arteries, always under angiographic control) and these allow to reach to the occlusion site and to catch/aspire (or both simultaneously) the clot that obstructs the cerebral artery.

SR technique is based on the catch of the clot though dedicated devices (stent-like retrievers) which can be deployed and re-sheathed after having trapped the clot through their struts. CA is based on the navigation of large bore aspiration catheters until the proximal surface of the clot and a continuous aspiration, performed either manually of through a mechanical pump, and allows to engage the clot inside of the aspiration catheter and to remove it by simple aspiration. Recently, their combined use (SR+CA) which is resumed in the CoT, showed similar results in terms of effectiveness, without however showing a superiority compared to SR alone (*Lapergue et al., 2019*).

Recent Randomized Controlled Trials (RCTs) showed the significant benefit of MT for patients with LVOs of the anterior circulation (*Jovin TG et al., 2015; Saver et al., 2015; Goyal M et al., 2015; Campbell et al., 2015*). Furthermore, also patients with posterior circulation AIS seem to benefit from MT (*Tao C et al., 2022; Li C et al., 2022*), although previous trials weren't able to show its superiority compared to the best medical management.

The aim of MT is to achieve the recanalization of the occluded artery rapidly, safely and completely. The number of MT procedures is constantly growing throughout the world and in France about 7500 procedures/year are performed.

1.5 Patients selection

As aforementioned, RCTs showed the evidence of the benefit of MT in AIS treatment as well as the need to properly select patients to treat.

Indeed, some subgroups of patients seem not to get a benefit from MT, which determines the condition of a technical success (the recanalization of the occluded artery) without achieving a favorable clinical result. This condition has been described in the literature as "futile recanalization". Currently, the rate of futile recanalization is reported to be between 45 and 55% (*Goyal M, 2016; van Horn N et al., 2021*), meaning that almost half of the patients treated by MT will not have a favorable clinical outcome. A possible explanation of this phenomenon could be provided by an inappropriate patients' selection. During the last years we observed a progressive widening of the indications to MT in terms of temporal window, age limit and clot location. On the other side, a larger number of patients have had access to MT compared to the last decade.

Patients' selection is currently performed through MRI (in particular in France and Switzerland) and more widely through CT scan (in most European and US countries). These imaging methods allow to assess the extension of the ischemic lesion, through the ASPECT score (**Fig.1**), the localization and the length of the occlusion as well as the presence of a collateral circulation at the moment of the treatment. A new paradigm of AIS management is currently being proposed by some recent on-

going and concluded trials, such as DIRECT ANGIO (*Riou-Comte N et al., 2021*), WE-TRUST (*https://www.wetrust-study.com/*), which are investigating the superiority of the arrival of the patients directly to the Angiosuite (the operating room where MT is performed) rather than passing through the MRI/CT scan screening.

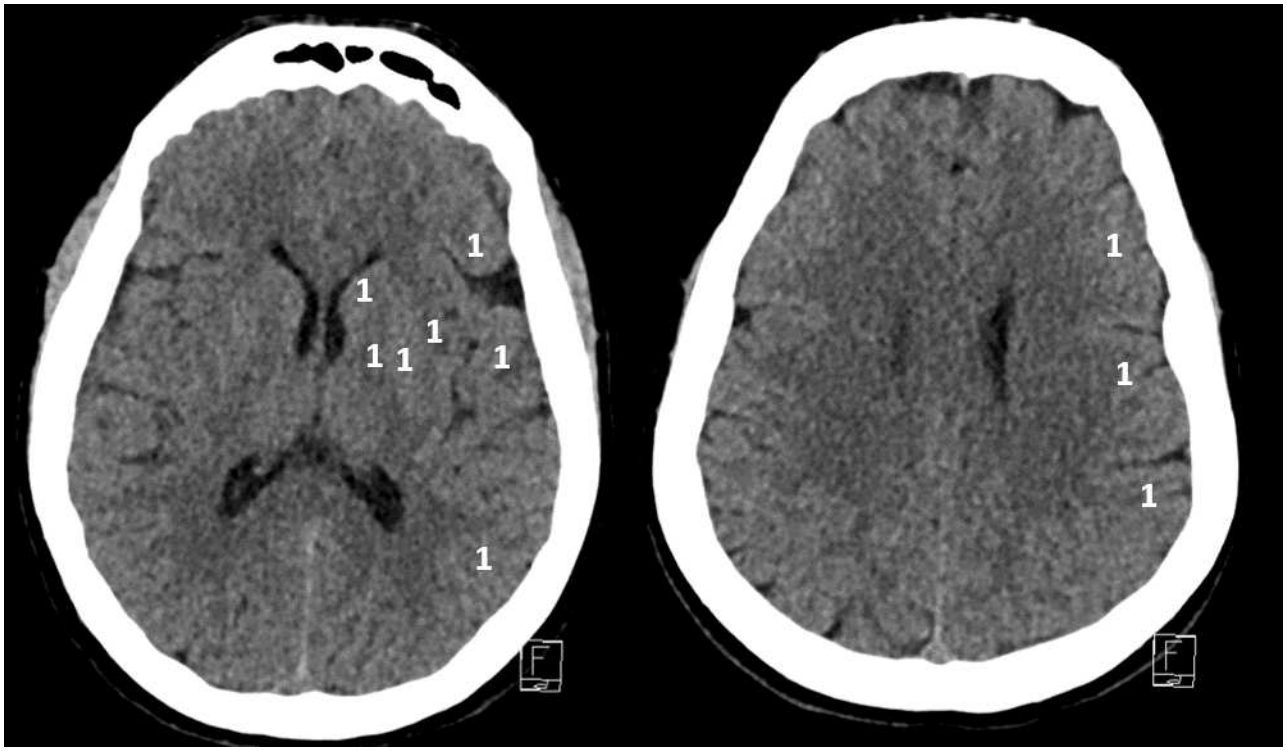


Fig. 1. *The Alberta Stroke Program Early CT (ASPECT) score: a 10-points scale used to assess the extension of the ischemic lesion. The ASPECT score is widely used and it can be applied to both MRI and CT scan.*

In this model, which includes patients admitted in the early phases of AIS (before 4.5 hours) and within severe neurological deficits, the Digital Subtraction Angiography (DSA) would acquire a central role as a selection tool for patients to treat, since it provides real-time information about the extension of the collateral circulation.

Moreover, it has been clearly showed that patients with LVOs and limited ischemic lesions represent the best target for MT and IVT in order to achieve a favorable clinical outcome (*Nogueira RG et al., 2017; Consoli A et al., 2016*), while patients with larger ischemic lesions and treated in very late windows represent those subgroup for which a clear response has not been provided yet and an ongoing clinical trial, IN EXTREMIS (*https://www.inextremis-study.com/*), will hopefully provide solid data about this issue.

1.6 The assessment of the collateral circulation

As previously mentioned, collateral circulation assumes a central role in patients' selection.

Collateral circulation (CC) has been widely described in the literature (*Mangiafico et al., 2014; Consoli et al., 2016; Rocha M et al., 2017; Qian J et al., 2020*) although its hemodynamic characteristics remain still largely unknown.

CC could be defined as a retrograde vascular supply of the cerebral circulation in a territory which cannot be fed because of the occlusion of the artery that normally vascularize defined cerebral areas. CC develops thanks to pre-existing anastomoses between the cortical arteries of neighbor territories (i.e. in case of occlusion of the MCA, the CC develops through anastomoses between the cortical branches of the MCA and the arteries of the ipsilateral Anterior Cerebral Artery – ACA. **Fig.2.**

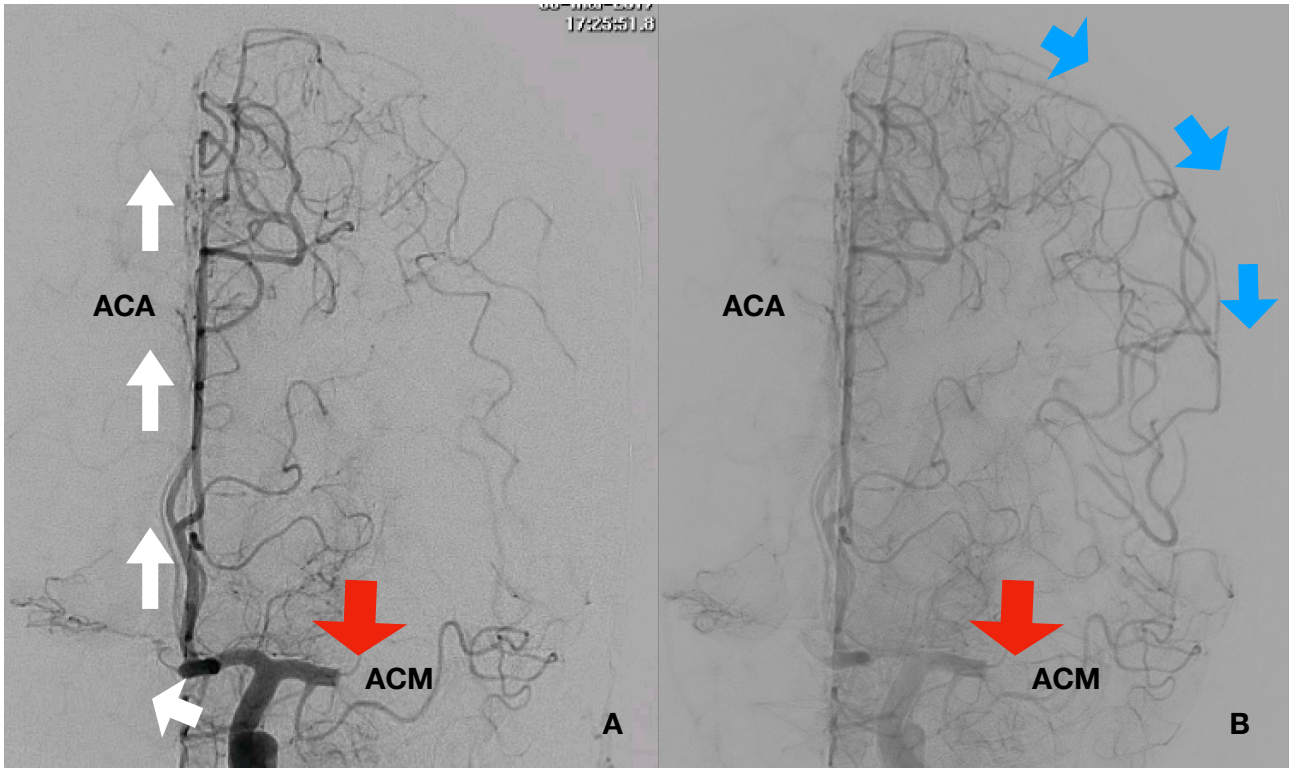


Fig.2 *Antero-Posterior early arterial phase (A) and late arterial phase (B) of a pre-treatment angiographic run during a MT procedure (from the candidate's Master 2 project). The occlusion of the left Middle Cerebral Artery (MCA - ACM, artère cérébrale moyenne in the figure) is observed (red arrow) and the collateral circulation activates through the Anterior Cerebral Artery (ACA, white arrows, A), whose cortical branches retrogradely anastomose with cortical MCA branches (blue arrows, B). Arrows show the direction of the blood flow highlighting the retrograde flow of the collateral circulation.*

From a physiopathologic point of view, CC reflects the expression of what we could name the "hemodynamic reserve" of the brain during ischemia. Previously reported studies showed how the development of CC is definitely individual and subjective (*Khatri R et al., 2011; Seyman E, et al. 2016*).

Currently, both CT-Angiography with a multiphase acquisition protocol (*Menon et al., 2015*) and MR-Angiography (*Hartkamp MJ, et al. 1999, Kim HJ et al., 2020*) could provide useful information about the extension of CC, however without providing further information about the qualitative measurement of the collateral vessels.

On the other side, the DSA, which is performed through the injection of iodine contrast mean directly into the artery, allows to provide a more sensitive assessment of CC in terms of extension and effectiveness, basing on its dynamic profile (*Consoli A et al., 2016; Mangiafico S et al., 2013*).

1.7 The role of the collateral circulation in AIS

The endovascular treatment of AIS is continuously evolving. The new devices, stent-like retrievers, net aspiration catheter, new angiographic machines, are considered among the most important technological novelties in the neuroradiological field, both diagnostic and interventional. However, such technical developments need to be associated to the evolution of the comprehension and understanding of the disease.

When we consider the anatomy of the cortical and subcortical arteries, we can observe how the cortical arteries which run on the pial surface of the brain give rise to the penetrating arterioles. These arterioles feed the microcirculation which is mainly constituted by the capillaries located in the cerebral cortex and in the sub-cortex (**Fig.3**).

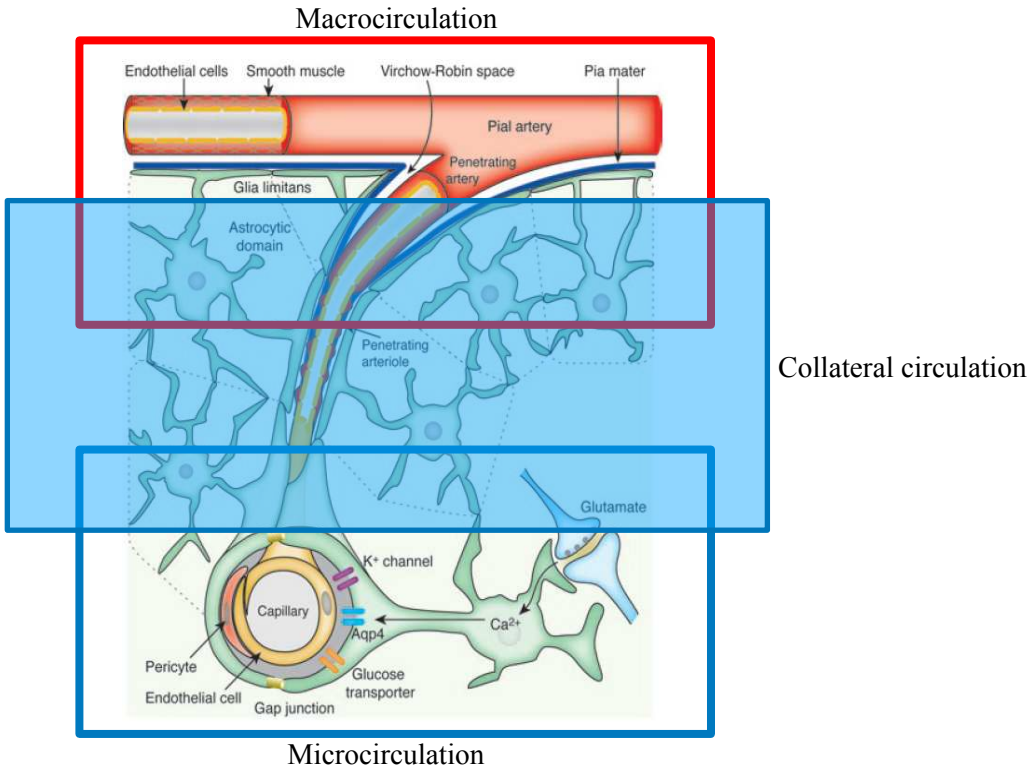


Fig 3. *The anatomy of cortical pial arteries and of the microcirculation (adapted from Iadecola, C., Nedergaard, M. Glial regulation of the cerebral microvasculature. Nat Neurosci* ***10,*** *1369–1376 (2007). https://doi.org/10.1038/nn2003).*

The microcirculation is responsible for the cerebral autoregulation and, therefore, for the maintenance of the perfusion of the cortex and of the subcortical area. In case of AIS with a LVO, the perfusion of the microcirculation can be maintained through some anastomoses that occur between the cortical arteries of two neighbor vascular territories (*Iadecola et al., 2007; Kunz A et al., 2009*).
These anastomoses, which constitute the CC, provide a retrograde filling of the penetrating arterioles and of the microcirculation and, consequently, the maintenance of the cerebral perfusion during the occlusion of an artery (*Iadecola et al., 2007*).
It is possible to argue that the CC intervenes between a Macro-circulation, meant as the cortical cerebral circulation (the cortical and pial arteries and the penetrating arterioles) and a microcirculation, intended as the cortical network of capillaries which is responsible for autoregulation. Indeed, some Authors pointed out the CC as a "modulator" for the vascular autoregulation response and for some specific hemodynamic phenomena such as the neurovascular coupling (*Vasquez HE et al., 2021*).
When an infarcted territory is retrogradely perfused through the CC it can be maintained in a "stunned" condition and since the autoregulation can be assured by the CC this part of the brain can be considered as salvageable in case of recanalization of the occluded artery.
Oppositely, if the CC is not present, the territory which is not fed by the occluded artery will rapidly evolve to necrosis with a definitive loss of function of that area even in case of a complete recanalization of the occluded artery.

Indeed, is we consider that the recanalization rates and the capacity of clot retrieval have exponentially increased up to 90% of the cases, favorable clinical outcomes are still permanently observed up to 45-55%. The aforementioned "futile recanalizations" reflect the impairment between the technological development and the stagnation of the understanding of the physiopathology of AIS.

Therefore, CC has been proposed as a plausible explanation to this phenomenon, since the presence of this retrograde circulation allows the brain to be fed during the period of the occlusion of the cerebral artery and a certain level of cerebral perfusion can be maintained during the ischemia.
On the other hand, the lack of this CC is associated with a poor and critical perfusional status of the brain without a clinical benefit for patients treated by MT (*Consoli A et al., 2016; Mangiafico S et al., 2013*).

These concepts can be resumed in the definition of the “slow” and “fast progressors”. Indeed, patients with good collaterals have been reported to achieve good clinical outcomes even in late temporal windows (*Liebeskind et al., 2022*) mainly because they harbored a good CC. The physiopathological explanation would lay in the effect of collaterals to maintain a level of cerebral perfusion during the ischemia, sustaining the ischemic penumbra and, therefore, the possibility to rescue the brain tissue from necrosis, even in patients treated in late windows, determining a slow progression of the ischemia (*Rocha et al., 2017, Mohammaden MH et al., 2022*).

1.8 Hemodynamics of cortical arteries and evaluation of cerebral blood flow velocity

The understanding of the hemodynamics of the cortical arteries of the brain is still limited. Pressure values and measurement of blood flow in this region still derives from measurements performed during microsurgical procedures after craniotomy and which were performed using microprobes in patients without LVOs (*Carter PL et al. 1978; Bederson et al. 1995*).
However, currently no data are provided in case of AIS and during an arterial occlusion, when we could assist to the activation of the cortical anastomoses which provide a retrograde cortical circulation.

Several papers focused on the issue of the measurement of blood flow velocity in cerebral arteries with non-invasive methods such as CT-Angiography or MR-Angiography (*Thierfelder KM et al., 2015; Menon BK et al., 2013; Smit EJ et al., 2013*), whereas the assessment directly performed on the DSA remains still limited (*Muehlen et al., 2019*).

Several groups focused on the correlation between the CC and perfusional imaging (*Galinovic I, et al., 2018, Cortijo E, et al. 2014*) and more recently on the dynamic evaluation of collateral vessels, in particular using dedicated scores such as the Cortical Veins Opacification score (COVES), which were applied either on CT-Angiography or on MR/CT-Perfusion (*Faizy et al., 2021; Faizy et al, 2021; Singh et al. 2022*)**.**

Section II - PREFATORY RESULTS

2. PREFATORY RESULTS

2.1. The CAPRI Study

The impact of the CC for AIS had already been extensively investigated in the literature. Several Authors had highlighted the unpredictable aspect of the development of these cortical anastomoses, since no correlations were found with age, sex or related vascular risk factors (*Lazzaro MA et al., 2011; Arsava EM et al., 2014, Christoforidis et al., 2020*).

Although the concept of CC was anatomically clear, no explanation had been provided concerning the role of CC in the physiopathology and in the early 2010s the evolution of the perfusional assessment in the setting of AIS was starting to be settled.
It had frequently be recalled how CC would represent the expression of the perfusional status of the brain at the moment of the ischemia, suggesting the role of a vascular "reservoir" to supply a vascular territory which was not fed by the related occluded artery (*Consoli A et al., 2016*).
However, no clear proof of a correlation between CC and the perfusional status had been provided at that time.
After having published a novel grading scale for CC (the Careggi Collateral Score, CCS) directly based on the 2D-angiograms (*Mangiafico S et al., 2013*), I had the possibility to coordinate a multi centric collaborative group that included five high-volume Italian centers focused on Interventional Neuroradiology and a renowned European institution, the Karolinska Institutet in Stockholm.

This collaborative group aimed to investigate the correlation between patients with AIS of the anterior circulation that were screened by using CT-Perfusion, which provided perfusional color-maps showing the extension of the ischemic core (the brain part that would not have been rescued even in case of a complete recanalization) and of the ischemic penumbra (the salvageable cerebral tissue), and DSA at the moment of the procedure of MT.
The results of this analysis were published in the *Journal of NeuroInterventional Surgery.*

The main hypothesis was that high grades of CCS, meaning a good collateral status, were associated with favorable perfusional patterns, such as small ischemic cores and large ischemic penumbras. This hypothesis was analyzed in the paper: *CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study,* published in the Journal of Neurointerventional Surgery in 2016.

The results of the CAPRI Study showed that a clear correlation between the collateral grade and the perfusional status of the brain could be established.

The perfusional status had been evaluated mainly on the CBV (Cerebral Blood Volume) color-maps which were a sensitive marker of the ischemic core, according to the literature (*Cortijo E et al., 2014*) and the extension of the ischemic core was assessed using the ASPECT score.

Finally, we could observe that patients with a good collateral status were more likely to be associated with significantly higher rates of favorable clinical outcomes (**Fig. 4**).

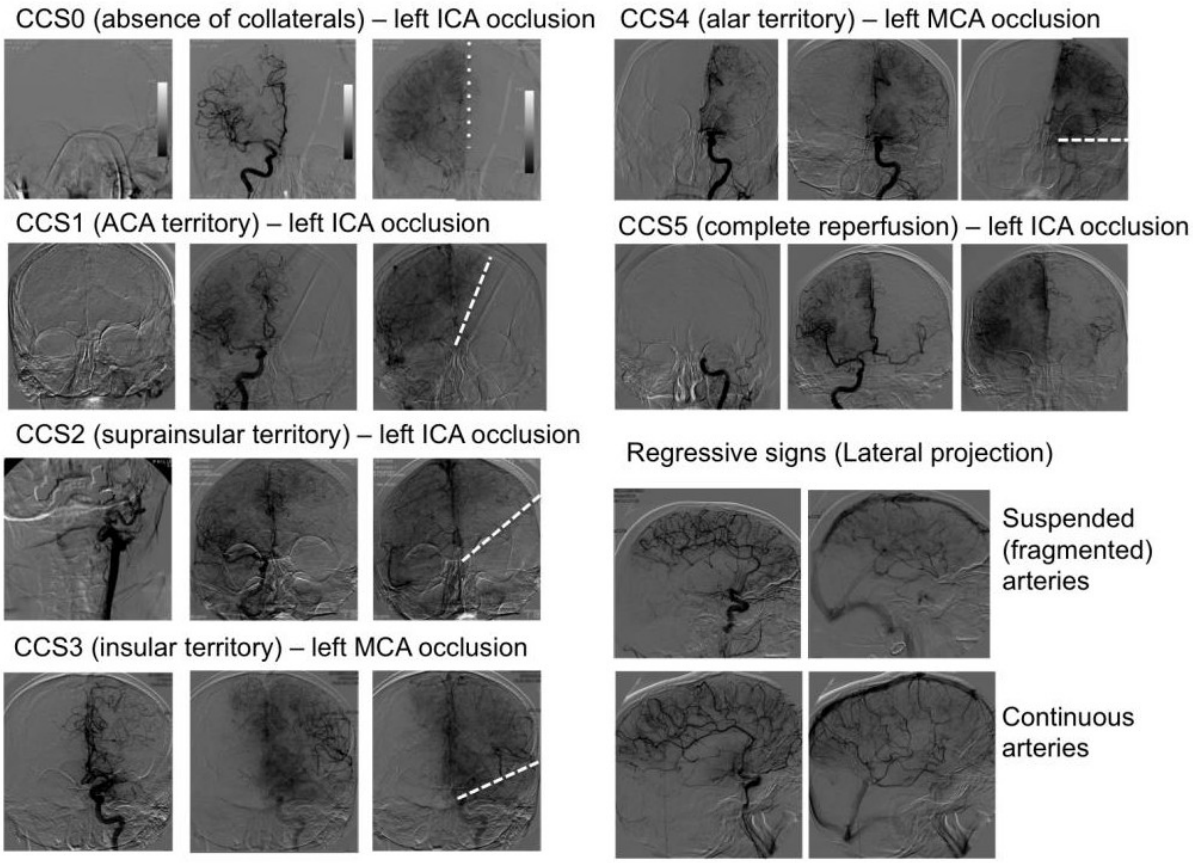


Fig. 4. *The Careggi Collateral Score introduced in 2013 to assess the collateral circulation directly on Digital Subtraction Angiography (image from the Supplemental material of Consoli A***,** *Andersson T, Holmberg A, Verganti L, Saletti A, Vallone S, Zini A, Cerase A, Romano D, Bracco S, Lorenzano S, Fainardi E, Mangiafico S; CAPRI Collaborative Group. CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study. The paper was published in the Journal of Neurointerventional Surgery (JNIS) in 2016. J Neurointerv Surg. 2016 Dec;8(12):1211-1216.. The score provided a semiquantitative evaluation of collateral vessels (in the anteroposterior projection) and a qualitative evaluation (in the lateral projection). In particular, the latter was assessed through the "suspended artery sign", first described in 2013 by Mangiafico et al.*

ORIGINAL RESEARCH

CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study

Arturo Consoli,[1] Tommy Andersson,[2,3] Ake Holmberg,[3] Luca Verganti,[4] Andrea Saletti,[5] Stefano Vallone,[4] Andrea Zini,[6] Alfonso Cerase,[7] Daniele Romano,[7] Sandra Bracco,[7] Svetlana Lorenzano,[8] Enrico Fainardi,[5] Salvatore Mangiafico,[1] on behalf of the CAPRI Collaborative Group

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/neurintsurg-2015-012155).

For numbered affiliations see end of artide.

Correspondence to
Dr A Consoli, Interventional Neuroradiology Unit, Careggi University Hospital, Largo Palagi 1, 4th floor CTO, Firenze 50134, Italy; onemed21@gmail.com

Received 6 July 2015
Revised 23 December 2015
Accepted 29 December 2015

To cite: Consoli A, Andersson T, Holmberg A, *et al*. *J NeuroIntervent Surg* Published Online First: [*please include* Day Month Year] doi:10.1136/neurintsurg-2015-012155

ABSTRACT

Background The purpose of this study was to evaluate the correlation between a novel angiographic score for collaterals and CT perfusion (CTP) parameters in patients undergoing endovascular treatment for acute ischemic stroke (AIS).

Methods 103 patients (mean age 66.7±12.7; 48.5% men) with AIS in the anterior circulation territory, imaged with non-contrast CT, CT angiography, and CTP, admitted within 8 h from symptom onset and treated with any endovascular approach, were retrospectively included in the study. Clinical, neuroradiological data, and all time intervals were collected. Careggi Collateral Score (CCS) was used for angiographic assessment of collaterals and the Alberta Stroke Program Early CT Score (ASPECTS) for semiquantitative analysis of CTP maps. Two centralized core laboratories separately reviewed angiographic data, whereas CT findings were evaluated by an expert neuroradiologist. Univariate and multivariate analysis were performed considering CCS both as an ordinal and a dichotomous variable.

Results 37/103 patients (35.9%) received intravenous tissue plasminogen activator. Median (IQR) ASPECTS was 9 (6–10) for admission CT, 9 (5–10) for cerebral blood volume (CBV) maps, 3 (2–3) for mean transit time maps, 3 (2–4), for cerebral blood flow maps, and 5 (3–7) for CTP mismatch. Univariate analysis showed a significant correlation between CCS and ASPECTS for all CTP parameters. Multivariate analysis confirmed an independent association only between CCS and CBV (p=0.020 when CCS was considered as a dichotomous variable, p=0.026 with ordinal CCS).

Conclusions A correlation between angiographic assessment of the collateral circulation and CTP seems to be present, suggesting that CCS may provide an indirect evaluation of the infarct core volume to consider for patient selection in AIS.

INTRODUCTION

All of the recent randomized controlled trials[1–3] on the treatment of acute ischemic stroke (AIS), although with different results, highlighted a well known issue: not all patients with AIS benefit from endovascular treatment, and this may also be due to different selection criteria. The neuroimaging approach based on CT perfusion (CTP) maps is constantly developing in AIS as well as interest in the study of collaterals, and it has been postulated that CTP findings may be related to the collateral circulation.[4 5] Conversely, although some authors have demonstrated an impact of collaterals on clinical outcome in AIS[6–13] and proposed angiographic (digital subtraction angiography (DSA) or CT angiography (CTA)) scales, no grading system for the assessment of collateral circulation can be considered definite and/or commonly accepted.[14]

The aim of this study was to evaluate the correlation between the collateral circulation, assessed with a recently proposed new angiographic score, the Careggi Collateral Score (CCS),[12 13] and CTP findings in patients undergoing endovascular treatment after AIS.

METHODS

Study subjects

Between January 2010 and June 2012, we retrospectively evaluated 431 consecutive patients with AIS in four experienced centers. Of these, 103 patients with AIS in the anterior circulation territory due to a major occlusion imaged with non-contrast CT (NCCT), CTA, and CTP within 8 h from symptom onset, not eligible for or non-responders to intravenous tissue plasminogen activator, and treated with any endovascular approach, were included in the study. A fifth site had the role of study coordinator center. Exclusion criteria are reported in online supplementary figure S1. The study received the approval of the local institutional review board of each participating center.

Clinical assessment

National Institutes of Health Stroke Scale (NIHSS) score at admission, 24 h after symptom onset, and at discharge was assessed in all patients. Clinical outcome at 3 months was measured using the modified Rankin Scale (mRS) by in-person visit or telephone interview; mRS ≤2 and >2 were defined as good and poor outcomes, respectively.

CT acquisition, processing, and analysis

NCCT, CTA, and CTP were performed at admission, on a 64 slice CT scanner (GE Medical System, Milwaukee, Wisconsin, USA) (for details, see online supplementary material). NCCT was repeated at 24–48 h. The extension of early

ischemic changes was evaluated on NCCT at onset using the Alberta Stroke Program Early CT Score (ASPECTS) methodology. ASPECTS was also used to measure the final infarct extension on follow-up NCCT at 24–48 h after symptom onset. All CTP scans were assessed using a commercially available delay sensitive deconvolution software (CT Perfusion 3; GE Healthcare, Waukesha, Wisconsin, USA), which ran on an imaging workstation (Advantage Windows; GE Healthcare). As described elsewhere,[15–18] CTP ASPECTS was calculated using cerebral blood flow (CBF??), cerebral blood volume (CBV) and mean transit time (MTT) maps (for details, see online supplementary material). CTP ASPECTS mismatch was considered as CBV ASPECTS minus MTT ASPECTS.[19] The type of hemorrhagic transformation was classified according to the European Cooperative Acute Stroke Study II criteria. The extent of intracranial thrombus was assessed on admission CTA by the Clot Burden Score.[20]

Endovascular treatment

Patients were treated by means of thrombectomy with stent-like retrievers and loco-regional fibrinolysis alone or in combination. All time intervals were recorded (onset to intravenous treatment, onset to groin puncture, time of procedure, and onset to reperfusion) and considered for statistical analysis. Procedure related adverse events were classified as follows: (a) subarachnoid hemorrhage secondary to arterial perforation; (b) migration of thrombus in areas not previously involved; and (c) arterial dissection.

Angiographic assessment

Angiographic assessment of leptomeningeal collaterals was performed with a complete study of the anterior circulation, in anteroposterior and laterolateral projections, by using prolonged injections (including late venous phases until visualization of venous sinuses) through both internal carotid arteries and, when possible, at least one of the two vertebral arteries, according to the methodology adopted in CCS development (see online supplementary figure S2).[12] For details, see online supplementary material. In this study, we used CCS as both a dichotomous (0–2: poor collaterals; 3–5: good collaterals) and an ordinal variable. Last anteroposterior and laterolateral runs were used to evaluate the final reperfusion, assessed with the Thrombolysis in Cerebral Infarction grading system.[21]

Core radiological laboratories

Two different core radiological laboratories were identified to analyze separately DSA studies (angiographic core laboratory) and an expert neuroradiologist with 20 years of experience analyzed NCCT, CTA, and CTP. For details, see online supplementary material.

Statistical analysis

Results were expressed as percentage for categorical variables, with proportions calculated by dividing the number of events by the total number of patients, excluding missing or unknown cases, and as median (IQR) or mean (±SD) for continuous variables. As appropriate, the c^2 or Fisher's exact test, and the Student's t test or the Mann–Whitney U test were used to compare categorical and continuous variables between the two groups. Spearman's correlation coefficients (Spearman's r) were derived to quantify the association between CCS as an ordinal variable and CTP parameters. Multivariate linear regression modeling was used to adjust for the effects of potential confounders and to evaluate whether CCS independently predicted CTP parameters. Variables with a univariate association with CCS at a p value of ≤0.10 were included in the relative multivariate models plus other potential predictors of perfusion deficit, independent of their univariate p value, such as age. Multivariate binary and ordinal logistic regression analyses were used to evaluate whether CCS was an independent predictor of functional outcome at 3 months. Receiver operating characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC) and hence cut-offs for CCS and ASPECTS parameters for predicting poor outcome (mRS >2). The independent effect of both radiological and clinical variables on mRS was calculated using multivariate logistic regression analyses, incorporating all covariates with p≤0.10 on univariate analysis. Finally, in order to verify whether a particular combination of poor collaterals and low ASPECTS was associated with poor outcome, interaction terms between CCS and each of the ASPECTS cut-offs were created and included in a binary logistic regression model for outcome to evaluate which had the highest predictive power. A two tailed p value of <0.05 was considered significant. All statistical analyses were performed with SPSS statistical package (SPSS V.22 Inc, Chicago, Illinois, USA).

RESULTS

Of 431 consecutive patients, 328 were excluded and 103 patients were included in the analysis. No significant differences in baseline characteristics were found between patients excluded and those included in the study. Demographic and baseline characteristics of the included 103 patients, overall and by CCS groups, are reported in table 1.

Median CCS was 3 (IQR 2–4) and good collaterals, as defined by CCS 3–5, were observed in 75/103 (72.8%). Interobserver agreement for the assessment of CCS performed by the angiographic core laboratory was kappa 0.83. Median ASPECTS was 9 for admission CT, 9 for CBV maps, 3 for MTT maps, 3 for CBF maps, and 5 for CTP mismatch. Recanalization, as indicated by Thrombolysis in Cerebral Infarction 2b-3, was achieved in 64.1% of cases. Favorable outcome (mRS 0–2) at 3 months and mortality were observed in 47.6% and 6.8% of cases, respectively. Overall, patients with good collaterals (CCS 3–5), compared to those with poor collaterals (CCS 0–2), had a lower NIHSS at baseline (p=0.002) and at discharge (p<0.001), a higher proportion of middle cerebral artery M1 proximal/distal segment occlusions, a lower proportion of internal carotid artery occlusions (p=0.001), a higher admission CBV (p=0.010), and mismatch (p=0.021) ASPECTS (table 1). CCS, used as an ordinal variable, showed a significant correlation with all CTP parameters measured with ASPECTS, indicating that good collaterals were related to the presence of higher CBV (Spearman's r=0.25; p=0.013), CBF (0.22; p=0.027), MTT (0.21; p=0.039), and CTP mismatch (0.21; p=0.032) ASPECTS and, hence, with a smaller brain tissue perfusion deficit. When we included CCS in the multivariate linear logistic regression models for each of the CT perfusion parameters (CBV, MTT, CBF, and CTP mismatch ASPECTS), CCS was a significant independent predictor only for CBV ASPECTS as both a dichotomous (model 1) and ordinal variable (model 2), indicating that good collaterals predicted a higher CBV ASPECTS (table 2).

The r^2 and adjusted r^2 were 0.52 and 0.50, respectively, for model 1, and 0.52 and 0.49, respectively, for model 2. More patients with good collaterals achieved a favorable outcome (mRS 0–2) compared with those with poor collaterals (60.0% vs 14.3%, p<0.001) (table 1, figure 1). In multivariate binary

Table 1 Baseline and follow-up characteristics of all patients and association with CCS 0–2 vs CCS 3–5

	All (n=103)	CCS 0–2 (n=28)	CCS 3–5 (n=75)	p Value
Age	66.7 (12.7)	67.4 (12.9)	66.4 (12.6)	0.705
Sex, female	53/103 (51.5)	13/28 (46.4)	40/75 (53.3)	0.533
Pre-stroke mRS 0–1	98/103 (95.1)	27/28 (96.4)	71/75 (94.7)	0.711
Vascular risk factors				
Hypertension	63/102 (61.8)	20/27 (74.1)	43/75 (57.3)	0.125
Diabetes mellitus	13/102 (12.7)	4/27 (14.8)	9/75 (12.0)	0.741
Atrial fibrillation	39/103 (37.9)	10/28 (35.7)	29/75 (38.7)	0.783
Prior stroke/TIA	10/102 (9.8)	4/27 (14.8)	6/75 (8.0)	0.449
Smoking, current	22/103 (21.4)	9/28 (32.1)	13/75 (17.3)	0.103
Pre-stroke medications				
Anticoagulants	16/102 (15.7)	7/27 (25.9)	9/75 (12.0)	0.121
Other hospitals	50/85 (58.8)	10/22 (45.5)	40/63 (63.5)	0.139
IV tPA	37/103 (35.9)	8/28 (28.6)	29/75 (38.7)	0.342
Neurological status				
Baseline NIHSS	16 (12–20)	19.5 (12.75–22.75)	16 (10–19)	0.045
NIHSS at 24 h	11.5 (4–18)	18 (10–20.5)	8 (4–15)	0.002
NIHSS at discharge	7 (2.25–16.75)	17 (8–19)	5 (1.5–12)	<0.001
Time intervals				
Onset to tPA	120 (85–175)	158 (150–180)	105 (85–171.25)	0.404
Onset to groin	258 (197–392.5)	298 (198–400)	255 (192–393.75)	0.209
Duration of procedure	76 (42–129.25)	91 (43–140.5)	68 (41.75–111.75)	0.234
Time to revascularization	348 (258–478.5)	417 (293.5–617.5)	330 (251–464)	0.147
Time of discharge				0.445
<24 h	14/83 (16.9)	1/20 (5.0)	13/63 (20.6)	
24–48 h	21/83 (25.3)	6/20 (30.0)	15/63 (23.8)	
48–72 h	4/83 (4.8)	1/20 (5.0)	3/63 (4.8)	
>72 h	44/83 (42.7)	12/20 (60.0)	32/63 (50.8)	
Procedures				0.450
Thrombectomy	78/103 (75.7)	20/28 (71.4)	58/75 (77.3)	
IA tPA	15/103 (14.6)	6/28 (21.4)	9/75 (12.0)	
Thrombectomy + IA tPA	10/103 (9.7)	2/28 (7.1)	8/75 (10.7)	
Admission CT ASPECTS	9 (6–10)	8 (6–10)	9 (6.75–10)	0.213
Vessel occlusion				0.001
MCA M1 (proximal/distal)	81/103 (78.6)	16/28 (57.1)	65/75 (86.7)	
ICA (infra/supraclinoid ICA; tandem ICA-MCA; T-siphon)	22/103 (21.4)	12/28 (42.9)	10/75 (13.3)	
Admission CTA-CBS	6 (4–8)	6 (3.25–8)	7 (5–7)	0.221
Admission CTP ASPECTS				
CBV ASPECTS	9 (5–10)	6 (5–10)	9 (6–10)	0.010
MTT ASPECTS	3 (2–3)	2 (1–3)	3 (2–3.25)	0.169
CBF ASPECTS	3 (2–4)	2 (1–3)	3 (2–4)	0.299
CTP ASPECTS mismatch (MTT-CBV)	5 (3–7)	4 (2–6)	6 (4–7)	0.021
24–48 h-CT ASPECTS	8 (5–9)	7 (4–9)	8 (6–10)	0.382
Infarct growth	0 (−2; 0)	−0.50 (−3.0; 0)	0 (−2; 0)	0.705
Side, right	57/103 (55.3)	14/28 (50.0)	43/75 (57.3)	0.505
CCS				
0	3/103 (2.9)			
1	5/103 (4.9)			
2	20/103 (19.4)			
3	48/103 (73.8)			
4	25/103 (24.3)			
5	2/103 (1.9)			
CCS	3 (2–4)	…	…	…
CCS 3–5	75/103 (72.8)	…	…	…
TICI				0.153
0	12/103 (11.7)	7/28 (25.0)	5/75 (6.7)	
1	4/103 (3.9)	1/28 (3.6)	3/75 (4.0)	
2a	21/103 (20.4)	5/28 (17.9)	16/75 (21.3)	
2b	30/103 (29.1)	7/28 (25.0)	23/75 (30.7)	
3	36/103 (35.0)	8/28 (28.6)	28/75 (37.3)	

Continued

Table 1 Continued

	All (n=103)	CCS 0–2 (n=28)	CCS 3–5 (n=75)	p Value
TICI 2b-3	66/103 (64.1)	15/28 (53.6)	51/75 (68.0)	0.174
Revascularization	88/97 (90.7)	21/25 (84.0)	67/72 (93.1)	0.230
Complications				0.753
SAH	2/103 (1.9)	0	2/75 (2.7)	
Thrombus migration	3/103 (2.9)	1/28 (3.6)	2/75 (2.7)	
Carotid stenting occlusion	1/103 (1.0)	0	1/75 (1.3)	
Outcome measures				
Early neurological improvement (≤4 NIHSS)	54/100 (54.0)	10/26 (38.5)	44/74 (59.5)	0.065
Early neurological deterioration (≥4 NIHSS or death)	14/100 (14.0)	4/26 (15.4)	10/74 (13.5)	0.754
Hemorrhagic transformation	20/96 (20.8)	7/24 (29.2)	13/72 (18.1)	0.246
ECASS II classification				0.169
HI1	7/96 (7.3)	2/24 (8.3)	5/72 (6.9)	
HI2	4/96 (4.2)	0	4/72 (5.6)	
PH1	6/96 (6.3)	3/24 (12.5)	3/72 (4.2)	
PH2	3/96 (3.1)	2/24 (8.3)	1/72 (1.4)	
SICH/ECASS II	4/96 (4.2)	1/24 (4.2)	3/72 (4.2)	1.0
mRS at 3 months				0.002
0	4/103 (3.9)	0	4/75 (5.3)	
1	23/103 (22.3)	1/28 (3.6)	22/75 (29.3)	
2	22/103 (21.4)	3/28 (10.7)	19/75 (25.3)	
3	20/103 (19.4)	9/28 (32.1)	11/75 (14.7)	
4	17/103 (16.5)	6/28 (21.4)	11/75 (14.7)	
5	10/103 (9.7)	4/28 (14.3)	6/75 (8.0)	
6	7/103 (6.8)	5/28 (17.9)	2/75 (2.7)	
mRS 0–2	49/103 (47.6)	4/28 (14.3)	45/75 (60.0)	<0.001
mRS 0–1	27/103 (26.2)	1/28 (3.6)	26/75 (34.7)	0.001
Death	7/103 (6.8)	5/28 (17.9)	2/75 (2.7)	

Continuous variables are reported as mean (SD) or median (IQR), as appropriate. Proportions are reported as percentages.
ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBS, Clot Burden Score; CBV, cerebral blood volume; CCS, Careggi Collateral Score; CTA, CT angiography; CTP, CT perfusion; ECASS, European Cooperative Acute Stroke Study; HI, hemorrhagic infarction; IA, intra-arterial; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; MTT, mean transit time; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; SICH, symptomatic intracerebral hemorrhage; TIA, transient ischemic attack; TICI, Thrombolysis in Cerebral Infarction; tPA, tissue plasminogen activator.

logistic regression analysis, CCS was an independent predictor of favorable outcome (OR 9.78, 95% CI 2.55 to 37.45; p=0.001). The shift analysis confirmed CCS as an independent predictor of functional outcome at 3 months as both a dichotomous (estimate: −1.389, 95% CI −2.291 to −9.487; p=0.003) and a categorical (estimate: −1.104, 95% CI −1.741 to −0.466; p=0.001) variable. Mortality was significantly lower for patients with CCS 3–5 (2.7% vs 17.9%; p=0.007) (table 1).

The optimal accuracy and cut-off points for CCS and baseline ASPECTS parameters (CT, CBF, CBV, MTT, and CBV–MTT mismatch) regarding 3 month mRS were defined in the ROC curve analyses. As reported in figure 2, CCS ≤2 had the highest AUC (0.70, 95% CI 0.60 to 0.80; p=0.001) with an overall performance significantly superior to other parameters, followed by MTT ASPECTS ≤2 (0.62, 95% CI 0.51 to 0.73; p=0.037). CT ASPECTS ≤7, CBF ASPECTS ≤2, and CBV ASPECTS ≤5 had an AUC of 0.60, but they did not reach the nominal statistical significance. Univariate analyses for poor outcome performed using the cut-offs individuated by ROC curve analysis, showed that low ASPECTS parameters, suggesting a larger ischemic brain injury, and poor collaterals, were associated with mRS >2 (CCS ≤2, p<0.001; MTT ASPECT ≤2, p=0.021; CT ASPECTS ≤7, p=0.049; CBF ASPECTS ≤2, 0.077; and CBV ASPECT ≤5, p=0.065). However, after multivariate adjustment, only CCS ≤2 remained as an independent predictor of mRS score 3–5 (OR 9.58, 95% CI 2.49 to 36.88; p=0.001). Clinical independent predictor was baseline NIHSS score (OR, 1.21; 95% CI 1.10 to 1.33; p<0.001). In order to verify whether a particular combination of poor collaterals and low ASPECTS was associated with poor outcome (mRS >2), interaction terms between CCS ≤2 and each of the ASPECTS parameter cut-offs were created. All were significantly associated with poor outcome on univariate analysis, but after adjustment in a binary logistic regression analysis, only the combination of CCS ≤2 and CBF ASPECTS ≤2 was an independent predictor of poor outcome (OR 6.49, 95% CI 1.14 to 36.84; p=0.035).

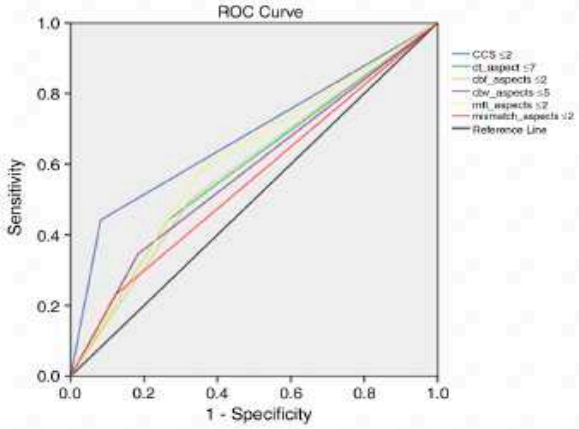
DISCUSSION

Revascularization of the occluded vessel(s) currently represents the most important goal in patients with AIS. Nevertheless, in approximately 20–25% of patients who achieve recanalization, it is found to be futile.[22] Therefore, clarifying the association between collaterals and CTP findings could improve our ability to select patients for stroke treatment, given the value of the collateral circulation[6–11] and CTP ASPECTS[15 17 18] in predicting outcome. In addition, CTP seems to be able to differentiate between infarct core and ischemic penumbra as, according to the classical 'penumbral hypothesis', areas with low CBV and low CBF or high MTT (CBF or MTT/CBV match) correspond to the core, while those with normal CBV and low CBF or high MTT (CBF or MTT/CBV mismatch) refer to the penumbra.[23 24] Although this assumption has been challenged by the demonstration that CBF better approximates the extent of the infarct core than CBV,[25] the potential of the MTT/CBV mismatch

Table 2 Multivariate linear regression analysis for cerebral blood volume ASPECTS with CCS as the dichotomous variable (0–2 vs 3–5) (model 1) and as the ordinal variable (model 2)

	B	β coefficient	95% CI for B	p Value
Model 1				
CCS	0.977	0.173	0.157 to 1.797	0.020
Previous stroke/TIA	−1.352	−0.164	−2.539 to −0.164	0.026
Baseline NIHSS	−0.067	−0.166	−0.128 to −0.007	0.030
Admission CT ASPECTS	0.616	0.477	0.427 to 0.806	<0.001
CBS	0.335	0.282	0.164 to 0.506	<0.001
Model 2				
CCS	0.417	0.166	0.052 to 0.783	0.026
Previous stroke/TIA	−1.462	−0.177	−2.647 to −0.276	0.016
Baseline NIHSS	−0.064	−0.157	−0.125 to −0.002	0.042
Admission CT ASPECTS	0.623	0.483	0.433 to 0.813	<0.001
CBS	0.346	0.291	0.175 to 0.517	<0.001

Adjusted for age, previous stroke/TIA, baseline NIHSS, admission CT ASPECTS, CBS, and CCS.
ASPECTS, Alberta Stroke Program Early CT Score; CBS, Clot Burden Score; CCS, Careggi Collateral Score; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.



Baseline ASPECTS perfusion parameters	AUC	95% CI	P	Cut-off point
CCS	0.70	0.60-0.80	0.001	≤2
CT ASPECTS	0.60	0.50-0.71	0.072	≤7
CBF ASPECTS	0.59	0.48-0.70	0.116	≤2
CBV ASPECTS	0.60	0.49-0.71	0.080	≤5
MTT ASPECTS	0.62	0.51-0.73	0.037	≤2
CBV-MTT mismatch ASPECTS	0.56	0.45-0.68	0.278	≤2

Figure 2 Receiver operating characteristic (ROC) curves analysis of the Careggi Collateral Score (CCS) and the Alberta Stroke Program Early CT Score (ASPECTS) parameters as predictors of poor outcome (modified Rankin Scale score >2). AUC, area under the curve; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time.

model in the selection of patients for reperfusion therapies was recently confirmed.[26]

In addition, although infarct core and ischemic penumbra are commonly identified using specific CTP thresholds,[23 24] it has been repeatedly demonstrated that the application of ASPECTS to CTP maps can be useful to accurately describe the extent of irreversible and reversible ischemic damage, which are indicated by CBV and CBF or MTT ASPECTS, respectively.[15 16 18 19] Of relevance, a connection between MTT and CBV CTP maps and collaterals has also been found.[4 5] On the other hand, most of the existing angiographic classifications have mainly focused on the quantitative extension of the collateral circulation,[21 27 28] without taking into account its qualitative features. Only the ASITN classification[21] differentiated between 'slow' and 'rapid' collateral flow according to the time of collateral filling.

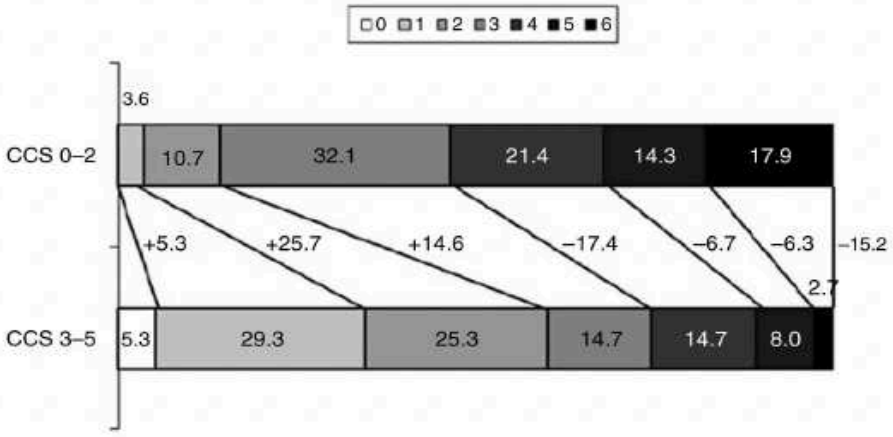


Figure 1 Distribution of the modified Rankin Scale (mRS) score at 3 months by the Careggi Collateral Score (CCS). Note the shift to a favorable outcome with good collaterals. The numbers at the lines and in the table indicate differences in the proportion of patients (%) who attained a particular score on the mRS between good (CCS 3–5) and poor (CCS 0–2) collaterals.

mRS score	Difference between good (CCS 3–5) and poor (CCS 0–2) collaterals (%)
0	+5.3
1	+25.7
2	+14.6
3	−17.4
4	−6.7
5	−6.3
6	−15.2

For these reasons, we sought to investigate the relationships between CTP data and collaterals using CTP ASPECTS methodology and a novel angiographic grading scale (CCS) that considers an immediate and easily applicable semiquantitative and, overall, qualitative assessment of the collateral circulation. The correlation between collaterals and CTP results should be based on the concept of pial reperfusion: the more extended and efficient the retrograde leptomeningeal reperfusion, the higher the number of areas that may be maintained in a condition of potentially reversible critical hypoperfusion. In our study, univariate analysis showed a significant correlation between CCS, considered as an ordinal variable, and all perfusion parameters (CBV, MTT, CBF ASPECTS as well as CTP ASPECTS mismatch). As a higher ASPECTS corresponds to smaller ischemic brain damage and, conversely, a lower ASPECTS is related to a larger brain tissue perfusion defect, these findings suggest that good collateral flow is associated with better perfusion at the level of ischemic tissue and vice versa. However, multivariate analysis demonstrated a significant association only between pure CCS and CBV ASPECTS, while no correlation was observed with the other perfusion parameters, indicating that CCS is an independent predictor of CBV ASPECTS.

Our findings are partially concordant with recent publications reporting a strong correlation between high relative CBV and good collaterals assessed by CTP source images (CTP-SI), confirming that CBV is a predictor of excellent collateral status.[4] However, to our knowledge, no studies focusing on the correlation between angiographic assessment of collaterals and CTP parameters have been reported in the literature.

Based on these observations, we are tempted to speculate that areas judged to have absent/incomplete and complete filling by CCS may correspond to regions of reduced and preserved CBV visualized on CTP, respectively. The extent of poor or no opacification identified by CCS and the volume of CBV deficit may reflect the infarct core size. Conversely, the low correlation between CCS and CTP ASPECTS mismatch suggests that the collateral grading system is not able to describe the amount of penumbral tissue. Collectively taken, our findings seem to suggest that the combination of CBV ASPECTS and CCS could be useful in the selection of AIS patients for endovascular therapy. In fact, a low CBV ASPECTS with poor collaterals (CCS 0–2) may identify 'critical' patients who do not benefit from revascularization and in whom recanalization could prove to be futile. The value of the association between CTP ASPECTS and CCS as a promising tool in the selection of AIS patients for endovascular treatment was further stressed by the demonstration that the only interaction which independently predicted poor outcome was between CBF ASPECTS ≤ 2 and CCS ≤ 2.

This study was affected by several limitations. First, the retrospective nature, the relatively small sample size, and the preliminary selection of patients could weaken the consistency of our data. Second, our CTP studies were performed with a delay sensitive deconvolution algorithm and one phase acquisition protocol, which lead to incorrect estimation of perfusion parameters due to the effects of bolus delay and truncation of time density curves, respectively.[29] Third, the actual correlation between CCS and CTP parameters remains to be elucidated because we did not use CBF to define infarct core and Tmax to delineate total hypoperfusion, as recently recommended.[30] Fourth, the specific limitations of the CCS should also be considered, such as the need for a contralateral injection in the case of internal carotid artery occlusion which implies an additional delay during procedural DSA performance, lack of assessment of a potential supply from the posterior circulation and, finally, lack of a comparative assessment with other angiographic scales.[12 13]

CONCLUSIONS

In this study, we demonstrated a correlation between the grade of collateral circulation evaluated by a novel angiographic scale (CCS) and CTP CBV ASPECTS, indicating that CCS may be considered as a surrogate indicator of infarct core size. As CCS provides a fast and easily applicable assessment of collaterals as well as being an independent predictor of clinical outcome, the combination of CCS and CBV ASPECTS may be useful for the selection of AIS patients as candidates for endovascular reperfusion therapy, particularly for those referred from peripheral hospitals (stroke centers) to hub centers. Further prospective and multicenter studies in a larger patient population are warranted to verify this hypothesis.

Author affiliations
[1]Interventional Neuroradiology Unit, Careggi University Hospital, Florence, Italy
[2]Departments of Radiology and Neurology, AZ Groeninge, Kortrijk, Belgium
[3]Department of Neuroradiology, Karolinska University Hospital, and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[4]Department of Neuroradiology, Nuovo Ospedale Civile 'S Agostino-Estense', Modena, Italy
[5]Neuroradiology Unit, Azienda Ospedaliero-Universitaria of Ferrara, Cona, Ferrara, Italy
[6]Stroke Unit, Department of Neuroscience, Nuovo Ospedale Civile 'S Agostino-Estense', Modena, Italy
[7]Unit of Neuroimaging and Neurointervention, Policlinico 'Santa Maria alle Scotte,', Siena, Italy
[8]Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy

Acknowledgements The authors thank Dr Elizabeth Jenkins for helpful corrections to the manuscript.

Collaborators Andrea Rosi, Leonardo Renieri, Sergio Nappini, Nicola Limbucci, Guido Bigliardi, Maria Luisa Dell'Acqua, Onofrio Marcello, Luca Borgatti, Massimo Borrelli, Stefano Ceruti, Andrea Bernardoni, Marina Padroni, Carmine Tamborino, Alessandro De Vito, Cristiano Azzini, and Leonardo Capaccioli.

Contributors ACo and SM were responsible for the concepts of the study, coordinated the study group, and drafted and reviewed the different versions of the paper. EF, TA, and SM were involved in the core laboratories for CT and angiographic images. SL performed the statistical analysis. EF, TA, AH, AS, LV, SV, ACe, SB, DR, AZ, and all the collaborators of the CAPRI Collaborative Group, collected the cases and reviewed all versions of the drafted papers.

Competing interests None declared.

Ethics approval The study was approved by the local institutional review board of each participating center.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All supplementary data, including specifications about the study protocol and further analyses, have been submitted and are available as supplementary material.

REFERENCES

1 Berkhemer OA, Fransen PS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.
2 Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019–30.
3 Campbell BC, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;12:372, 1009–18.
4 Cortijo E, Calleja AI, García-Bermejo P, *et al*. Relative cerebral blood volume as a marker of durable tissue-at-risk viability in hyperacute ischemic stroke. *Stroke* 2014;45:113–18.
5 Keedy AW, Fischette WS, Soares BP, *et al*. Contrast delay on perfusion CT as a predictor of new, incident infarct: a retrospective cohort study. *Stroke* 2012;43:1295–301.
6 Bang OY, Saver JL, Buck BH, *et al*. Impact of collateral flow on tissue fate in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2008;79:625–29.
7 Bang OY, Saver JL, Kim SJ, *et al*. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. *Stroke* 2011;42:693–99.
8 Ribo M, Flores A, Rubiera M, *et al*. Extending the time window for endovascular procedures according to collateral pial circulation. *Stroke* 2011;42:3465–9.

9 Liebeskind DS, Tomsick TA, Foster LD, *et al*. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke* 2014;45:759–64.
10 Liebeskind DS, Jahan R, Nogueira RG, *et al*; SWIFT Investigators. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke* 2014;45:2036–40.
11 Marks MP, Lansberg MG, Mlynash M, *et al*. Effect of collateral blood flow on patients undergoing endovascular therapy for acute ischemic stroke. *Stroke* 2014;45:1035–9.
12 Mangiafico S, Consoli A, Renieri L, *et al*. Semi-quantitative and qualitative evaluation of pial leptomeningeal collateral circulation in acute ischemic stroke of the anterior circulation: the Careggi Collateral Score. *Ital J Ana Embryol* 2013;118:277–87.
13 Mangiafico S, Saia V, Nencini P, *et al*. Effect of the interaction between recanalization and collateral circulation on functional outcome in acute ischaemic stroke. *Interv Neuroradiol* 2014;6:704–14.
14 McVerry F, Liebeskind DS, Muir KW. Systematic review of methods for assessing leptomeningeal collateral flow. *AJNR Am J Neuroradiol* 2012;33:576–82.
15 Parsons MW, Pepper EM, Chan V, *et al*. Perfusion computed tomography: prediction of final infarct extent and stroke outcome. *Ann Neurol* 2005;58:672–9.
16 Lin K, Rapalino O, Law M, *et al*. Accuracy of the Alberta Stroke Program Early CT Score during the first 3 hours of middle cerebral artery stroke: comparison of noncontrast CT, CT angiography source images, and CT perfusion. *AJNR Am J Neuroradiol* 2008;29:931–6.
17 Psychogios M-N, Schramm P, Frölich AM, *et al*. Alberta Stroke Program Early CT Scale evaluation of multimodal computed tomography in predicting clinical outcomes of stroke patients treated with aspiration thrombectomy. *Stroke* 2013;44:2188–93.
18 Lum C, Ahmed ME, Patro S, *et al*. Computed tomographic angiography and cerebral blood volume can predict final infarct volume and outcome after recanalization. *Stroke* 2014;45:2683–8.
19 Lin K, Rapalino O, Lee B, *et al*. Correlation of volumetric mismatch and mismatch of Alberta Stroke Program Early CT Scores on CT perfusion maps. *Neuroradiology* 2009;51:17–23.
20 Puetz V, Dzialowski I, Hill MD, *et al*. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. *Int J Stroke* 2008;3:230–6.
21 Higashida RT, Furlan AJ, Roberts H, *et al*. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003;34:e109–37.
22 Goyal M. Poor clinical outcome despite successful arterial recanalization. What went wrong? How can we do better? *Neuroradiology* 2010;52:341–3.
23 Murphy BD, Fox AJ, Lee DH, *et al*. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. *Stroke* 2006;37:1771–7.
24 Wintermark M, Flanders AE, Velthuis B, *et al*. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke* 2006;37:979–85.
25 Campbell BCV, Christensen S, Levi CR, *et al*. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke* 2011;42:3435–40.
26 Prabhakaran S, Soltanolkotabi M, Honarmand AR, *et al*. Perfusion-based selection for endovascular reperfusion therapy in anterior circulation acute ischemic stroke. *AJNR Am J Neuroradiol* 2014;35:1303–8.
27 Christoforidis G, Mohammad Y, Kehagias D, *et al*. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol* 2005;26:1789–97.
28 Al-Ali F, Tomsick TA, Connors JJ, *et al*. Capillary index score in the interventional management of stroke trials I and II. *Stroke* 2014;45:1999–2003.
29 Konstas AA, Goldmakher GV, Lee TY, *et al*. Theoretic basis and technical implementations of CT perfusion in acute ischemic stroke, part 2: technical implementations. *AJNR Am J Neuroradiol* 2009;30:885–92.
30 d'Esterre CD, Fainardi E, Aviv RI, *et al*. Improving acute stroke management with computed tomography perfusion: a review of imaging basics and applications. *Trasl Stroke Res* 2102;3:205–20.

2.2. The preliminary results at CIC-IADI Laboratory

After the publication of the CAPRI study, several papers focused on the correlation between collaterals and cerebral perfusion (*Galinovic et al., 2018; Ginsberg MD, 2018, Menon BK, 2020*).

Furthermore, in the last 5 years several technical developments were introduced in the study of cerebral perfusion through CT or MR Perfusion-Weighted Imaging (PWI) and a large number of automated softwares have been released in order to calculate rapidly the cerebral perfusional status. These softwares, such as the RAPID® or the OLEA® software, allow to extrapolate a quantitative assessment of the ischemic core and the ischemic penumbra and to provide color maps almost in real time. On the other hand, no further advancements have been done concerning DSA, except for some sporadic attempts (*Muehlen et al., 2019*).

The main advantage of DSA is to provide a dynamic visualization of the intracranial circulation and of the CC thanks to the transit of the iodine contrast mean within the vessels. Contrast passes through the arteries, then to the capillaries and finally runs through the veins to be drained towards the heart and secondarily to the pulmonary circulation to be re-oxygenated. The algorithms used by the CT-Perfusion or MR-PWI are based on the same principle: after contrast injection, the transit time of the contrast itself is calculated and according to the different transit time in the cerebral areas a quantitative assessment is provided. Color-maps are generated according to the delay of transit of the contrast mean.

Intuitively, the transit time in a cerebral territory vascularized by an artery that is occluded will be much longer than the one measured in a territory where the feeding artery is patent. However, the presence of collateral vessels determines the maintenance of a certain amount of blood flow in the infarcted cerebral territory. This phenomenon is thought to support the concept of the ischemic penumbra: the cerebral territory receiving the blood flow through CC is maintained “stunned” and it remains salvageable if the occluded artery is properly recanalized.

However, it is known that several biochemical events occur at the level of the CC, such as in-situ thrombosis, platelets uncontrolled adhesion and distal migration of proximal emboli (downstream emboli). Therefore, one could argue that although a CC is present and extensively visible either on the non-invasive imaging methods (CT- or MR-Angiography) or directly on the DSA, the collaterals vessels could not be effective because of the aforementioned biological phenomena. Indeed, the thrombosis of these collaterals vessels would determine a slowdown in the CC, which could not provide the retrograde filling of the microcirculation (**Fig. 3**).

The concept of the effectiveness of CC represented the main target of my Master 2 project.
The aim of the Master 2 project was to focus on the analysis of the 2D angiograms acquired during the DSA, which represent the direct imaging method used to perform MT (**Fig. 5**).

Fig.5. *Screenshot from the title page of the Master 2 final thesis, focused on the assessment of flow velocity in cerebral cortical vessels directly on Digital Subtraction Angiography.*

Indeed, basing on the assumption that the visualization of the CC could provide useful information about the extension of the collateral vessels but on necessarily on their effectiveness, the goal was to build up an algorithm of segmentation to be applicable directly to the 2D-DSA images in order to analyze the flow velocity within the CC, which could be considered as a surrogate of the effectiveness of these collateral vessels.

Since the setting of a complex algorithm requires a considerable time, we had decided to focus the Master 2 objective on the first step of the process: the acquisition of the angiographic data. 2D-DSA images are acquires by the angiographic machine while a bolus of iodine contrast mean is injected.

In order to analyze a dynamic process, such as the visualization of the CC, we argued that the standard acquisition protocols currently used in the clinical practice could not be sufficiently informative.

In order to properly analyze DSA images we had primarily defined an "experimental" acquisition protocol for the DSA images to be compared to a "standard" acquisition protocol which is already set on the angiographic machines. The standard clinical protocols are based on a 2 frames/second frequency with a variable number of frames during the time intervals of the acquisition. The "experimental" protocol was made up of a 6 frames/second frequency with a variable but higher number of frames acquired during the time intervals of the acquisition. The experimental protocol is currently already available in the basic setup of angiographic machines, but not systematically used in standard care methods**.** The acquisition is limited to a single angiogram and therefore there is no modification of procedural time and not significant differences in terms of radiation exposure. The objective is to find an acquisition method that can provide sufficient acquisition rate in order to provide information of the contrast behavior to reflex the pre-treatment CC functionality. The CC functionality is therefore evaluated by the enhancement speed of the CC area by the contrast agent. Therefore, a first basic version of an algorithm for segmentation of vessels using Fussy C-means, which was capable to provide the perfusion-like curves according to the pixel opacification in the CC area, after the normalization of the results with the area of the involved brain hemisphere.

Clinical data and the angiographic runs of 10 patients with AIS secondary to the occlusion of the M1 segment of the MCA treated by MT at the Foch Hospital have been selected for the purpose of the study. All the patients were imaged through the experimental acquisition protocol. In order to compare the two protocols, we have simulated the standard protocol by subtracting a number of frames proportional to the cadence of the angiographic protocol. Finally the algorithm evaluated the DSA series acquired with the two different protocols and provided the perfusional curves which were obtained.

The local Ethical Committee at Foch Hospital had approved the use of the pseudonymized data of the patients and of the DSA data. Data corresponding to the two protocols lead to two different perfusional curves where the standard one shows an aliasing like behavior and might indicate different predictions of clinical outcomes.

A clinical analysis was performed in order to observe the impact of the visualization of CC on clinical outcomes, and in particular on the 3-months modified Rankin Scale (mRS, **Table 1**), a widely used scale to assess the functional independency at 3 months after the ischemic event.

Table 1. *The modified Rankin Scale.*

mRS score	Description
0	No symptoms at all
1	No significant disability, despite symptoms, able to carry out all usual duties and activities
2	Slight disability, unable to carry out all previous activities, but able to look after own affaires without assistance
3	Moderate disability, requiring some help (e.g. with shopping/managing affairs) but able to walk without assistance
4	Moderate severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Sever disability, bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Imaging analysis aspects

The workflow of the technical process is summarized in **Fig. 6**.

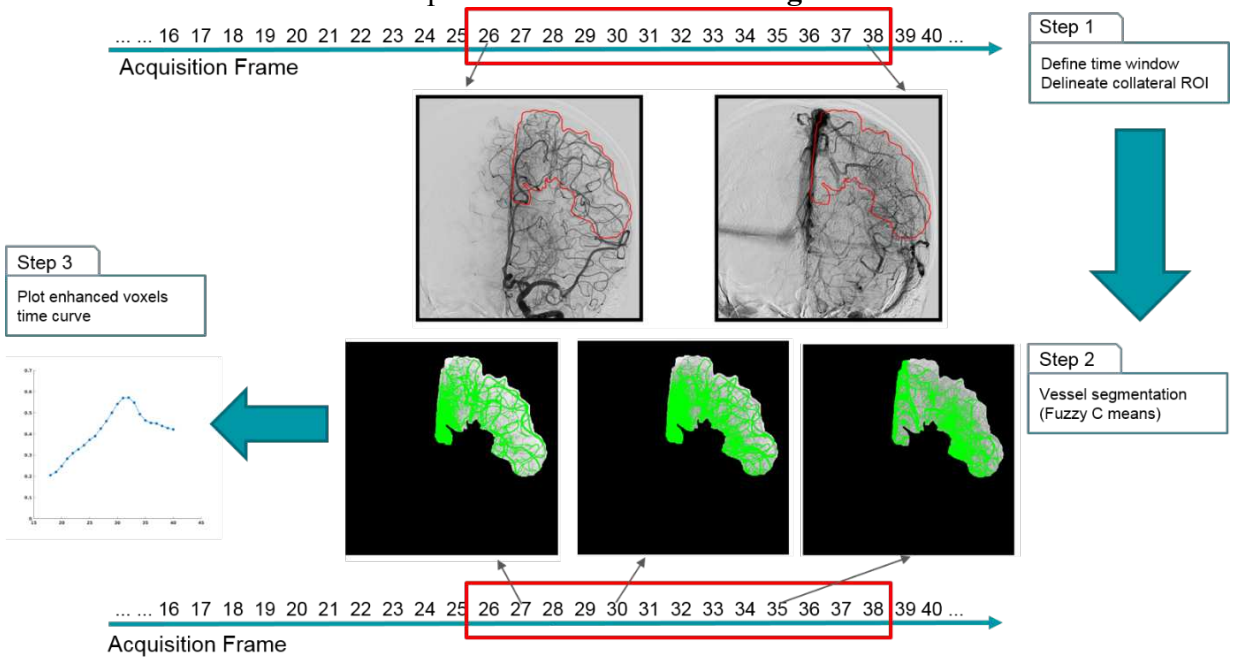


Fig. 6. *Post-treatment workflow. Phase 1: definition of the temporal window (time of interest, TOI) and of the collateral area (region of interest, ROI); Phase 2: segmentation of the opacified vessels in every frame of the TOI; Phase 3: production of the curve that plotted the number of enhanced vessels over time (perfusional curve).*

All the 2D DSA data were firstly manually segmented through the ITK-SNAP software (www.itk-snap.org) (*Yushkevich PA et al., 2006*). I have performed the manual segmentation of the collateral region and of the hemisphere area for each patient, carefully identifying the collateral vessels on the first frame where these were visible until the last frame.

Indeed, since DSA is a dynamic imaging method the progression of the contrast agent is observed in different circulatory phases, passing through the artery (arterial phase), capillaries (parenchymal/ capillary phases) and the veins (venous phase). The contrast enhancement changes were computed based on the segmentation of CC arteries which led to a time-enhanced artery perfusion curve.

Results and perspectives

We have observed that the perfusional curves obtained through the post-processing of the experimental protocol at 6 frames/second were more precise and contributive as compared to those obtained with a standard 2 frames/second protocol.

Intuitively, the experimental protocol provided a higher amount of data in a definite time window, which represents a major advantage to analyze CC, since this type of collateral circulation is visualized during the whole angiographic run and in some cases all along the three different phases (arterial, parenchymal and venous). Since the basic version of the algorithm is sensitive to the opacification of the vessels and to the pixel density modifications over time, a 6 frames/second acquisition protocol is associated with a higher number of vessels and pixel modification to analyze.

This effect determines the achievement of more precise perfusional curves, which is particularly adapted for a dynamic circulation visible over different time points (**Fig. 7**).

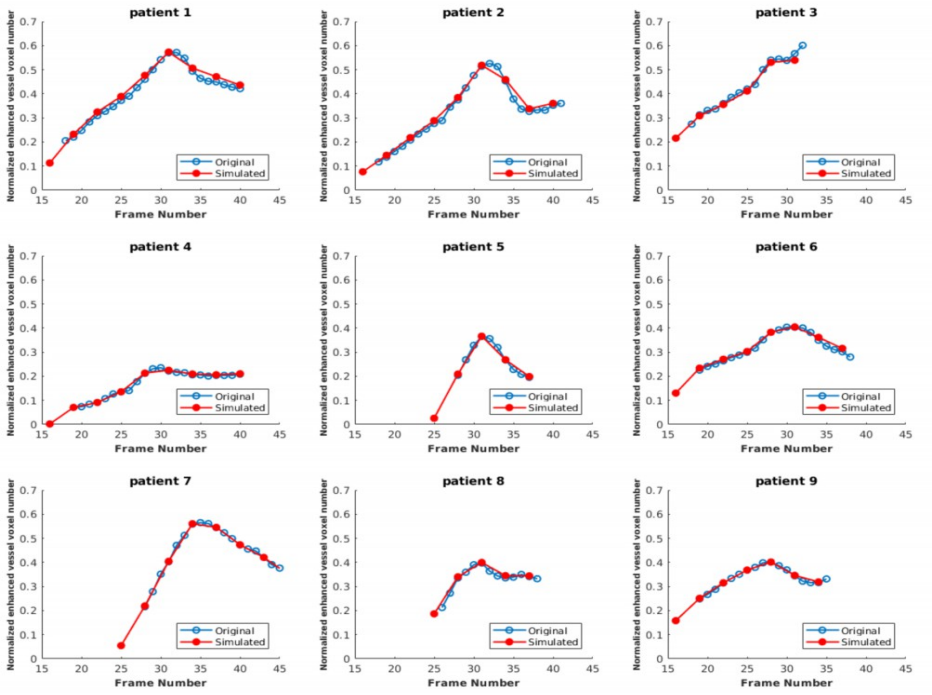


Fig. 7. *Results of the comparison of the perfusional curves obtained through the analysis of the angiograms provided by the experimental acquisition protocol (6 frames/second, blue dotted line) and the simulated standard one (after reconstruction at 2 frames/second, red dotted line).*

Furthermore, we had analyzed the clinical outcomes of the 10 patients included in the analysis. All the patients were completely or adequately recanalized, according to the modified Treatment In Cerebral Ischemia score (*Dargazanli C et al. 2018*) (mTICI score, **Table 2**).

Table 2. *The modified Treatment In Cerebral Ischemia score (mTICI score)*

mTICI	Description
Grade 0	No perfusion or anterograde flow beyond site of occlusion
Grade 1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimally filling of the normal territory
Grade 2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared to non-involved territories
Grade 2a	Some perfusion with distal branch filling of <50% of territory visualized
Grade 2b	Substantial perfusion with distal branch filling of ≥50% of territory visualized
Grade 2c	Near complete perfusion except for slow flow in a few distal cortical vessels, or presence of small distal cortical emboli.
Grade 3	Complete perfusion of normal filling of all distal branches

Although it is known that the recanalization grade is a strong predictor of a favorable clinical outcome, a certain number of patients do not reach functional independence after MT (about 45-55%) (*Goyal M, 2016; van Horn N et al., 2021*).

In this context, it was very interesting to notice that after having analyzed the perfusional curves obtained, two definite clusters of patients were recognizable (**Fig. 8**): the upper cluster, which included those patients with good clinical outcomes and the lower cluster regrouping those patients with high mortality rates and poor clinical outcomes. The main difference in these two small cohort of patients was the perfusional curve obtained after the analysis of the CC. Hence it may be plausible to use the shape of the perfusional curve as predictors for patient outcomes

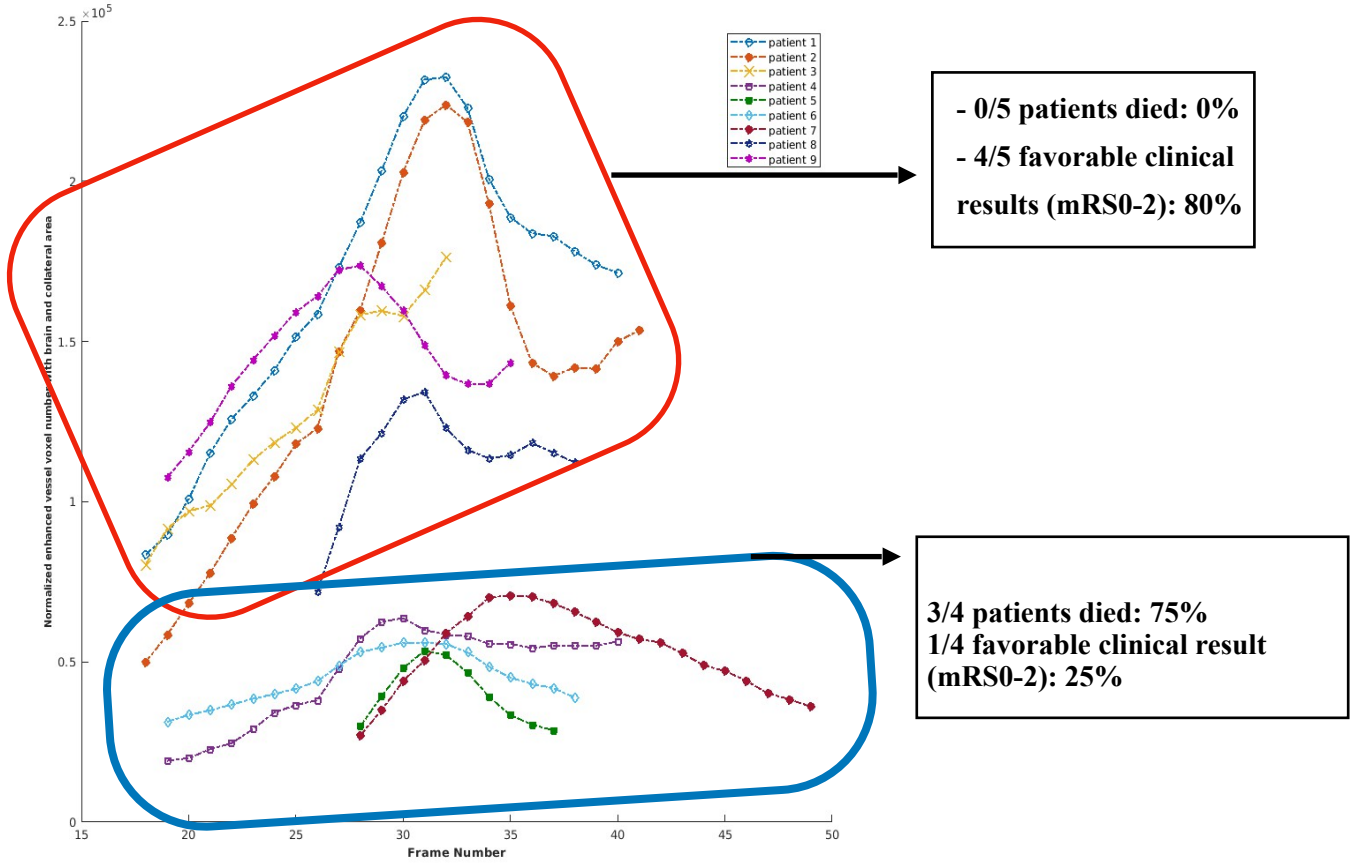


Fig. 8. *Graph showing the different behavior of the two identified clusters of patients according to the distribution of the perfusional curves after normalization (adapted and modified from the candidate's Master 2 project). The upper cluster (highlighted by the red rectangle) shows better clinical results (80% of favorable clinical outcomes and 0% of mortality) than the lower cluster (blue dotted rectangle: 25% of favorable clinical results and 75% of mortality). The main difference between the two clusters was based on the profile of the perfusional curve, which was more enhanced in the perfusional curves of the upper cluster, which showed a higher number of vessels opacified in the collateral area and therefore with effective collaterals.*

These preliminary results determined the first step of a rigorous methodological approach to the setting of a segmentation algorithm dedicated to the analysis of CC in patients with AIS.

Section III - PhD ENDPOINTS

3. CLINICAL RELEVANCE OF THE COLLATERAL CIRCULATION AS A PROGNOSTIC FACTOR IN ACUTE ISCHEMIC STROKE

The role of CC in determining favorable clinical outcomes has been widely described in the literature. Several papers have shown how collaterals are associated with favorable clinical outcomes after endovascular treatment (*Bang OY et al., 2008, Bang OY et al., 2011, Ribo M et al., 2011, Liebeskind et al., 2014, Consoli et al., 2016*), by enhancing the results of the recanalization after MT (*Mangiafico S et al., 2014, Liggins JT et al., 2015*), increasing the exposure of the clot to the IVT (*Seners P et al., 2019*), limiting the ischemic vascular damage (*Tong et al., 2018*), encouraging the dislodgment of the clot (*Leng X et al., 2015*).

Furthermore, good collaterals have also been associated with a lower risk of hemorrhagic transformation after recanalization (*Cao R et al., 2020; Hao Y et al., 2017*)**,** reducing the risk of growth and extension of the ischemic lesion as well as the risk of cerebral swelling and symptomatic intracerebral hemorrhages.

Considering the overall stroke population, it has been shown that about 45-55% of patients successfully treated by MT will not reach a functional independence (*Goyal et al., 2016, van Horn et al., 2021*). Among these, old patients, those with low baseline ASPECTS, those who are incompletely or who are lately recanalised and those where intraprocedural complications occurred are more likely not to benefit from MT. Patients with a good collateral profile are usually considered as the most suitable candidates for MT, since these are associated with less severe clinical conditions and with more limited ischemic lesions (*Consoli et al., 2016*). However, also patients with good collaterals may not benefit from MT, despite a favorable perfusional and clinical pattern, although a deep analysis of the factors which determine a poor outcome in this specific subgroup of patients has not been performed yet.

Therefore, this chapter was focused on the clinical relevance of the CC as a prognostic factor in AIS patients. In particular the aim was to investigate which factors can be associated with unfavorable outcomes in patients with a good collateral profile. This research question was approached in the UNCLOSE (**UNfavorable CLinical Outcomes in patients with good collateral Scores study)** Study, a retrospective analysis of a cohort of patients with a good CC, submitted to the *Journal of Neuroradiology*.

UNfavorable CLinical Outcomes in patients with good collateral Scores following Endovascular treatment for acute ischemic stroke of the anterior circulation: the UNCLOSE study.

Arturo Consoli[1,2], M.D., M.Sc., Marco Pileggi[1,3]*, M.D., A T M Hasibul Hasan[1,4], M.D., Alice Venier[1], M.D., Alessandro Sgreccia[1], M.D., Silvia Pizzuto[1], M.D., Oguzhan Coskun[1], M.D., Federico Di Maria[1], M.D., Luca Scarcia[1,5], M.D., Bertrand Lapergue[6], M.D., PhD, Georges Rodesch[1], M.D., PhD, Serge Bracard[2,7], M.D., Bailiang Chen[2], M.D. PhD.

**shared first co-authorship*

[1] Interventional and Diagnostic Neuroradiology Department; Foch Hospital, 92151 Suresnes, France

[2] CIC-IT IADI Laboratory, 1433, Inserm, CHRU de Nancy, Université de Lorraine, 54000 Nancy, France

[3] Diagnostic and Interventional Neuroradiology, Neurocenter of Southern Switzerland, EOC, 6900 Lugano, Switzerland.

[4] National Institute of Neurosciences and Hospital, 1207 Dhaka, Bangladesh

[5] Institute of Radiology, Università Cattolica del Sacro Cuore, 00168 Rome, Italy

[6] Departement of Neurology and Stroke Unit; Foch Hospital, 92151 Suresnes, France

[7] Interventional and Diagnostic Neuroradiology Department; CHRU de Nancy 54000 Nancy, France

Abstract

Background: Patients with acute ischemic stroke secondary to large vessel occlusions and good collaterals are frequently associated with favorable outcomes after mechanical thrombectomy (MT), although poor outcomes are observed also in this subgroup. We aimed to investigate the factors associated with unfavorable outcomes (mRS3-6) in this specific subgroup of patients. **Methods**: 219 patients (117 females, mean age: 70.6±16 y.o.) with anterior circulation stroke and good collaterals (ASITN/SIR grades 3-4), treated by MT between 2016-2021 at our institution were included in this study. Clinical files and neuroimaging were retrospectively reviewed. Univariate and multivariate analyses were performed to identify the predictors of unfavorable outcomes in the overall population (primary endpoint). Secondary endpoints focused on the analysis of the predic-tors of unfavorable outcomes in the subgroup of successfully recanalized patients, predictors of mortality and symptomatic intracerebral hemorrhages (sICH) in the overall population. **Results**: Poor outcome was observed in 47% of the patients despite the presence of good collaterals. Older age ($p<0.001$), baseline mRS2 ($p<0.001$), higher baseline NIHSS ($p<0.001$), longer onset-to-recanalization ($p=0.03$) and "groin-to-recanalization" times ($p=0.004$), no intravenous thrombolysis administration (no-IVT, $p=0.004$), >3 passes ($p=0.01$), partial recanalizations (mTICI0-2a; $p=0.002$), higher 24h-NIHSS ($p<0.001$) and sICH ($p<0.001$) were associated with the primary endpoint. The multivariate analysis showed an independent correlation between unfavorable outcomes and older age, higher 24h-NIHSS, 24h-ASPECTS, no-IVT and with secondary transfers. **Conclusions**: Despite good collaterals poor outcomes occurred in 47% of the patients. The main factors associated with unfavorable outcomes are comparable to those observed in patients with poor collaterals. Patients with good collaterals not receiving IVT were significantly associated with unfavorable outcomes, whereas FPE was not significantly correlated with clinical outcome in this specific cohort of patients.

Highlights

- A good collateral circulation is associated with favorable outcomes in patients with large vessel occlusions of the anterior circulation treated by mechanical thrombectomy. These patients are generally considered as the best candidates for the endovascular treatment.
- Unfavorable outcomes may occur in almost half of the patients with good collateral circulation (47% in our series)
- Predictors of unfavorable clinical outcome do not differ in patients with good collaterals as compared to those observed in the literature concerning patients with poor collaterals.
- The presence of good collaterals may not be sufficient to achieve favorable outcomes in patients with large vessel occlusions of the anterior circulation.
- Good collaterals should be considered as a supplemental reason to obtain fast and complete recanalizations.

Introduction

Good collaterals represent a hemodynamic reservoir for ischemic areas due to large vessel occlusions (LVOs). Their role has been widely described in the literature in terms of association with favorable clinical outcome,[1,2] of the modulation between "slow" and "fast progressors" [3,4] and of the reduction of the hemorrhagic transformation after mechanical thrombectomy (MT).[5] Therefore, patients with good collaterals are considered as the most suitable candidates for MT, although poor clinical outcomes are observed also in patients with a good collateral profile. The aim of this paper was to analyse the factors associated with poor clinical outcomes in patients with a potentially fa-vorable profile based on the presence of a good collateral circulation.

Materials and Methods

Study cohort

All consecutive patients with acute ischemic stroke of the anterior circulation who underwent me-chanical thrombectomy from January 1st 2016 to December 31st 2021 at our institution were retro-spectively analyzed from a prospectively collected, web-based registry (ETIS Registry, NCT03776877).

Variables and definitions

In the present study, the following data were reviewed and analyzed: age, sex, cardiovascular risk factors, baseline modified Rankin Scale (mRS), baseline National Institute of Health stroke scale (NIHSS) score, presence of hemorrhage or acute FLAIR signal abnormalities at baseline CT or MRI, CT or DWI-Alberta Stroke Program Early CT Score (ASPECTS), arterial occlusion site, pa-tient's direct admission to our comprehensive stroke center or to a primary stroke center with sec-ondary transfer ("drip and ship"), time metrics (onset-to-groin - OTG, onset-to-recanalization - OTR, groin-to-recanalization - GTR), intravenous thrombolysis administration, type of anesthesia, MT technique, number of passes, first pass effect (FPE) procedural complications, recanalization grade according to the modified Treatment in Cerebral Infarction (mTICI) scale, 24 hours-NIHSS and ASPECTS, hemorrhagic transfor-

mation and symptomatic intracerebral hemorrhage (sICH) accord-ing to the ECASS definition and 90-days mRS score. Standard recanalization grades definitions were used: partial (mTICI 0-2a), adequate (mTICI 2b-3) and almost complete/complete (mTICI 2c-3). Patients at admission were mainly images by MRI (>90%).

Ethical approval was obtained from the institutional review board, which waived for patient informed consent.

Inclusion and Exclusion Criteria

Inclusion criteria were: age ≥ 18, acute LVO in the anterior circulation (intracranial internal carotid and M1 or proximal M2 segments of the middle cerebral artery), and good collateral circulation which was defined as grades 3 and 4 of the American Society for Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale. [6]

Patients with tandem or multiple occlusions, with significant pre-stroke disability defined as modified Rankin Scale (mRS) >2, and patients with incomplete and unavailable follow-up data were excluded.

Collateral circulation assessment

Interventional images were retrospectively reviewed by an interventional neuroradiologist and an interventional neurologist with ≥5 years of experience in the neurointerventional field. Collateral circulation was assessed on the pre-thrombectomy angiographic study, with injection from ipsilateral ICA (for M1 and proximal M2 occlusions) or contralateral ICA and posterior circulation (for intra-cranial ICA occlusions). The ASITN/SIR scale was used for the evaluation. A third neurointerven-tionalist with >10 years of experience reviewed all the angiograms and resolved the disagreements. Kappa inter- and intra-observer agreement was calculated per grade and per dichotomization (grades 1-2 vs grades 3-4). Patients without an adequate pre-thrombectomy angiographic study to assess collateral circulations were excluded.

Endpoints

The primary endpoint was to investigate the factors associated with unfavorable outcomes defined as the lack of the achievement of a functional independence (mRS 3-6) at 90-days outpatient visit or telephone interview. Clinical evaluations were performed by certified stroke neurologists.

Secondary outcomes included the analysis of those factors associated with: unfavorable outcomes in patients adequately recanalized (defined as mTICI 2b-3), all-causes mortality at 90-days and post-procedural symptomatic intracerebral hemorrhage (sICH) in the overall population.

Supplementary specific analyses, such as the subgroup of patients recanalized with mTICI 2c-3, were performed in order to help with the interpretation of the results.

Statistical analysis

Statistical analysis was performed using descriptive evaluation with the median [interquartile] or mean ± standard deviation for continuous variables and frequency and percentage for categorical variables. Student's T-tests or Wilcoxon tests were performed for continuous variables depending to the number of patients in groups. For categorical variables, chi square test or Fisher's test were used when the expected value was less than 5. Those variables associated with the outcome in univariate analysis with a significance level below 0.2 were included in a multivariate logistic regression mod-el, which was adjusted for confounding factors. The odds ratios between factors and outcomes of their respective 95% confidence intervals were calculated. Stepwise backward multiple regression was performed to identify statistically significant predictors. All tests were bilateral with a 5% de-gree of significance. Statistical analysis was performed with the SAS 9.4 software.

Results

We reviewed 1419 patients with acute ischemic stroke due to LVO in the anterior circulation treat-ed by mechanical thrombectomy and 219 (females: 53.4%, mean age: 70.6 ±16 y.o.) patients were included in the final analysis after the application for the exclusion criteria. A flowchart of the study is provided in Fig.1. Kappa intra- and inter-observer agreement were respectively 0.61 and 0.69 per ASITN/SIR grade and 0.72 and 0.82 per dichotomization (grades 1-2 vs 3-4). An unfavorable outcome was observed in 103 patients (47%). The results of the univariate analysis related to the prima-ry and to the secondary endpoints are summarized respectively in Table 1 and Table 2, whereas Ta-ble 3 reports the multivariate analyses. Supplementary analyses are reported in Supplemental Tables 1-3.

Primary endpoint

In our population, a statistically significant correlation with an unfavorable clinical outcome was observed for patients with older age ($p<0.001$), baseline mRS2 ($p<0.001$), higher baseline NIHSS ($p<0.001$), longer onset-to-recanalization (OTR, $p=0.03$) and "groin-to-recanalization" times ($p=0.004$). IVT administration ($p=0.004$), number of passes <3 ($p=0.01$), a partial mTICI score (TI-CI 0-2a; $p=0.002$), a higher 24h-NIHSS and lower 24h-ASPECTS ($p<0.001$) and sICH ($p<0.001$). The multivariate analysis showed an independent correlation between unfavorable outcomes and older age, higher 24h-NIHSS, lower 24h-ASPECTS, no-

IVT administration and secondary transfers ("drip and ship" model).

Secondary endpoints

Factors associated with unfavorable outcome in patients with adequate recanalization are shown in Table 2 and did not differ from those identified for the primary endpoint at the univariate analysis, except for the OTR and the procedural time, which were not significantly associated.

In the sub-analysis performed on all-cause mortality at 90 days we observed that although older age ($p<0.001$), baseline mRS, baseline and 24h-NIHSS and 24h-ASPECTS ($p<0.001$), IVT administra-tion ($p=0.02$) and adequate recanalization ($p=0.01$) were significantly correlated, only older age, 24h-NIHSS and 24h-ASPECTS resulted independent predictors at the adjusted multivariate analy-sis (Table 3).

Furthermore, sICH were significantly correlated to baseline ASPECTS, longer procedures, FPE, a higher number of maneuvers, recanalization failures and 24h-NIHSS, whereas only 24h-NIHSS, 24h-ASPECTS and PH1-PH2 grades proved a statistical correlation at the multivariate analysis.

Discussion

Patients with good collaterals could be described as the best candidates for mechanical throm-bectomy. However, a non-negligible part of patients treated by MT does not reach functional inde-pendence after the endovascular treatment,[7] although patients with unfavorable outcomes show more frequently a poor collateral profile.[8] In our cohort, age (OR: 1.05, IC95%[1.02-1.09], $p=0.001$) and higher 24-hours NIHSS (OR: 1.23, IC95%[1.14-1.32], $p<0.001$) were some of the main predictors of poor clinical outcome (Table 1), which is in line with previously published pa-pers.[9] However, some Authors argued that age could have a different behavior which would be in favor of a preserved collateral status.[10] The mean age of this cohort was 70.6 ±16 y.o., which could be considered slightly higher than in other acute stroke cohorts. We aimed to analyze the im-pact of other factors that could explain the unfavorable clinical results in this specific subgroup of patients with good collaterals.

Collaterals and recanalization

The adequate recanalization of the occluded artery is widely known as an independent predictor of favorable clinical outcome, although about half of the patients with adequate-to-complete recanali-zation do not achieve a functional independence.[11] Our results showed that an adequate recanali-zation grade remains a strong predictor of favorable clinical outcome in patients with good collat-erals. The interaction between the recanalization grade and collaterals had already been investigated pre-

viously showing that collaterals enhance the effect of the recanalization, improving the clinical outcomes of recanalized patients.[12]

When we compared patients with favorable clinical outcomes and those with unfavorable ones, the rates of mTICI 2b-3 were high in both subgroups but significantly lower in the subgroup of patients with an unfavorable outcome (82% vs 95%, p=0.002; Table 1) independently from the endovascular technique used. Interestingly, neither the FPE nor the mTICI grade resulted as independent predic-tor of favorable outcome or a protective factor for mortality at the multivariate analysis (Table 3), however that could be explained by the selected population and the high recanalization rates in both subgroups. Thus, we observed similar results when we considered patients with mTICI 2c-3 grades (Supplemental Table 1). These results are in line with the physiopathological concept that collaterals supply the microcirculation in the ischemic territory during the arterial occlusion,[13] maintaining a sort of "hemodynamic reserve".[14]

Other possible explanations of the effectiveness of the association between collaterals and recanali-zation could be related to the mitigation of the ischemic vascular injury or the better exposition to thrombolytics agents [15] or to the higher chance of dislodgment of the clot.[12,16] Nevertheless, complete recanalizations may have a favorable impact on the collateral circulation itself, allowing the removal of the thrombotic material in the pial arterioles and in the capillary bed providing a proper supply of the microcirculation.[17]

Furthermore, we did not observe any differences concerning the type of anesthesia or the use of a balloon guide catheter (BGC) whereas the potential detrimental effect of general anesthesia was described in patients with poor or intermediate collaterals [18] and the BGC had previously been correlated with improved outcomes [19] unless a combined technique (stent retriever+aspiration) was used as a first-line strategy.[20] Moreover, intraprocedural complications were not associated with worse clinical outcomes since these were neither frequent nor clinically relevant in most of the cases. Indeed, mechanical vasospasm represented more than half of the reported complications without clinical consequences.

Collaterals and time

In our cohort, patients with unfavorable clinical outcomes were recanalized later with almost a 30-minutes difference in terms of onset-to-reperfusion (299.4 vs 270.4 minutes, p=0.03; Table 1). Sec-ondary transfers resulted significantly associated with unfavorable outcomes (OR: 4.41, IC95%[1.70-11.43], p=0.002) at the multivariate analysis whereas no differences were shown in terms of onset-to-groin. However, if we consider only patients with almost complete/complete re-canalization we observed that the impact of the secondary transfers was not significant (Supple-mental Table 1). The most significant difference was observed

in terms of procedure time, which was longer in patients with unfavorable outcomes (63.1 vs 46.3 minutes, p=0.004), although no dif-ferences were shown in terms of first-line endovascular technique or occlusion site. This datum could be explained by the higher number of passes performed in patients with poor clinical out-comes (2.7 vs 2, p=0.01, Table 1) or sICH (3.5 vs 2.3 minutes, p=0.01, Table 1), which is in line with previously reported series [21]. These results could suggest that despite good collaterals, a fast and complete recanalization must remain the goal of mechanical thrombectomy. Therefore, good collaterals should not be considered as a "time machine" that would provide a certain tolerance for long procedures.

The effect of the collateral circulation to maintain the cerebral perfusion during ischemia also in late temporal windows has already been described [22] as well as its role of modulator of the progres-sion of the ischemia.[23] Moreover, in our population we did not observe any significant difference in terms of clinical outcome between patients treated before and beyond 6 hours (mRS0-2: 56% vs 44%, p=0.19, Supplemental Table 2) although higher recanalization grades were obtained before 6 hours, which supports the hypothesis of a neuroprotective effect of good collaterals on the brain tissue in both early and late windows.

Collaterals and thrombolysis

The role of intravenous thrombolysis on collateral circulation remains still debated. Some Authors did not find any correlation between IVT and collaterals [24] while other papers had underlined the role of both fibrin [25] and platelets [26,27] in the development of the in-situ thrombotic phenome-na that can occur within the collateral vessels, particularly in the venous side.[17] Intravenous thrombolysis (mainly Alteplase according to the inclusion period) was significantly associated with favorable clinical outcomes with a protective effect observed at the multivariate analysis (OR:0.28, IC95%[0.11-0.73], p=0.009). There is currently no evidence that IV thrombolysis may have an ef-fect on collateral circulation, and these results could be explained by the significantly higher rate of patients with mTICI 2b-3 among those who received IV thrombolysis prior to mechanical throm-bectomy (Supplemental Table 3). The SWIFT DIRECT Trial [28] has recently shown that the asso-ciation IVT+MT provided better clinical outcomes compared to MT alone. However, in our cohort secondary transfers were significantly associated with unfavorable outcomes and it could be hy-pothesized that the transfer delays may be due to the IVT administration. Nevertheless, only 60% of the patients secondarily transferred to our institution had received IV thrombolysis at the Primary Stroke Centers (unpublished data).

Collaterals and hemorrhagic transformation

The rate of sICH was low (5.9%, 13/219) as one could expect in a selected population with good collateral scores. Indeed, poor collaterals are frequently associated with higher hemorrhagic rates after endovascular treatment.[5,29] In this cohort, lower baseline ASPECTS, partial or unsuccessful recanalizations (mTICI 0-2a) and longer procedures were associated with a higher rate of sICH. Indeed, patients with adequate and almost complete/complete recanalization had significantly higher 24h-ASPECTS ($p>0.001$, Tables 2-3, Supplemental Tables 1-2). This result is in line with previously published papers [30] which highlighted a sort of protective effect of collaterals to slow-down the extension of the ischemia, although in this specific cohort of patients with good collaterals and adequate recanalization we observed an unfavorable outcome in 47% of the cases.

Limitations

The retrospective nature of the analysis represents the main limitation of this study. However, we acknowledge also the fact that since the collateral circulation was assessed using the ASINT/SIR [6] scale and that the inter- and intra-observer agreement for this score could be quite poor,[8] although in this cohort we considered a dichotomous parameter since we included only patients with ASITN/SIR grades 3 and 4 and an excellent inter-observer agreement was recorded.

Furthermore, although the predictors of unfavorable outcome did not differ from those observed in overall stroke populations and already described in literature, this study represents, to the best of our knowledge, the first analysis specifically focused of this subgroup of patients, providing find-ings that could be potentially hypothesis-generating.

Conclusions

Unfavorable clinical outcomes were observed in 47% of patients following mechanical thrombecto-my despite good collaterals according to the ASITN/SIR classification. Although a good collateral circulation could allow to achieve functional independency also in patients treated in late temporal windows, partial recanalizations and longer procedures were associated with poor outcomes without resulting independent predictors, independently from the endovascular technique. FPE was not sig-nificantly correlated with clinical outcome. Intravenous thrombolysis increases the chance to achieve a good clinical outcome in patients with good collaterals without increasing the risk of hemorrhagic transformation.

Competing interests

None

Ethics approval statement

The local Institutional Review Board approved the data collection and analysis for this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data are available upon reasonable request to the corresponding author

References

[1] Gersing AS, Schwaiger BJ, Kleine JF, *et al.* Clinical Outcome Predicted by Collaterals Depends on Technical Success of Mechanical Thrombectomy in Middle Cerebral Artery Occlusion. *Journal of Stroke and Cerebrovascular Diseases* 2017;**26**:801–8. doi:10.1016/j.jstrokecerebrovasdis.2016.10.020

[2] Qian J, Fan L, Zhang W, *et al.* A meta-analysis of collateral status and outcomes of mechanical thrombectomy. *Acta Neurol Scand* 2020;**142**:191–9. doi:10.1111/ane.13255

[3] Rocha M, Jovin TG. Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke: Clinical and Research Implications. *Stroke* 2017;**48**:2621–7. doi:10.1161/STROKEAHA.117.017673

[4]Mohammaden MH, Haussen DC, Pisani L, *et al.* Characterizing Fast and Slow Progressors in Anterior Circulation Large Vessel Occlusion Strokes. *Interv Neuroradiol* 2022;:159101992210831. doi:10.1177/15910199221083100

[5] Cao R, Ye G, Wang R, *et al.* Collateral Vessels on 4D CTA as a Predictor of Hemorrhage Transformation After Endovascular Treatments in Patients With Acute Ischemic Stroke: A Single-Center Study. *Front Neurol* 2020;**11**:60. doi:10.3389/fneur.2020.00060

[6] Higashida RT, Furlan AJ. Trial Design and Reporting Standards for Intra-Arterial Cerebral Thrombolysis for Acute Ischemic Stroke. *Stroke* 2003;**34**. doi:10.1161/01.STR.0000082721.62796.09

[7] van Horn N, Kniep H, Leischner H, *et al.* Predictors of poor clinical outcome despite complete reperfusion in acute ischemic stroke patients. *J NeuroIntervent Surg* 2021;**13**:14–8. doi:10.1136/neurintsurg-2020-015889

[8] Ben Hassen W, Malley C, Boulouis G, et al. Inter- and intraobserver reliability for angiographic leptomeningeal collateral flow assessment by the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale. *Journal of NeuroInterventional Surgery* 2019;11:338-341.

[9] Arsava EM, Vural A, Akpinar E, *et al.* The Detrimental Effect of Aging on Leptomeningeal Collaterals in Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases* 2014;**23**:421–6. doi:10.1016/j.jstrokecerebrovasdis.2013.03.014

[10] Agarwal S, Scoffings DJ, Jones PS, *et al.* Interaction of age with the ischaemic penumbra, leptomeningeal collateral circulation and haemodynamic variables in acute stroke: a pilot study. *Journal of Neurology, Neurosurgery & Psychiatry* 2013;**84**:271–6. doi:10.1136/jnnp-2012-303258

[11]Goyal M, Menon BK, van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *The Lancet* 2016;**387**:1723–31. doi:10.1016/S0140-6736(16)00163-X

[12]Leng X, Fang H, Leung TWH, *et al.* Impact of Collateral Status on Successful Revascularization in Endovascular Treatment: A Systematic Review and Meta-Analysis. *Cerebrovasc Dis* 2016;**41**:27–34. doi:10.1159/000441803

[13]Kunz A, Iadecola C. Chapter 14 Cerebral vascular dysregulation in the ischemic brain.

In: *Handbook of Clinical Neurology*. Elsevier 2008. 283–305. doi:10.1016/S0072-9752(08)01914-3
[14]Consoli A, Andersson T, Holmberg A, *et al.* CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study. *J NeuroIntervent Surg* 2016;**8**:1211–6. doi:10.1136/neurintsurg-2015-012155
[15]Seners P, Roca P, Legrand L, *et al.* Better Collaterals Are Independently Associated With Post-Thrombolysis Recanalization Before Thrombectomy. *Stroke* 2019;**50**:867–72. doi:10.1161/STROKEAHA.118.022815
[16]Liggins JTP, Mlynash M, Jovin TG, *et al.* Interhospital variation in reperfusion rates following endovascular treatment for acute ischemic stroke. *J NeuroIntervent Surg* 2015;**7**:231–3. doi:10.1136/neurintsurg-2014-011115
[17]Tong L, Guo Z, Ou Y, *et al.* Cerebral venous collaterals: A new fort for fighting ischemic stroke? *Progress in Neurobiology* 2018;**163–164**:172–93. doi:10.1016/j.pneurobio.2017.11.001
[18]Liu D, Nie X, Pan Y, *et al.* Adverse Outcomes Associated With Higher Mean Blood Pressure and Greater Blood Pressure Variability Immediately After Successful Embolectomy in Those With Acute Ischemic Stroke, and the Influence of Pretreatment Collateral Circulation Status. *JAHA* 2021;**10**:e019350. doi:10.1161/JAHA.120.019350
[19]Blasco J, Puig J, Daunis-i-Estadella P, *et al.* Balloon guide catheter improvements in thrombectomy outcomes persist despite advances in intracranial aspiration technology. *J NeuroIntervent Surg* 2021;**13**:773–8. doi:10.1136/neurintsurg-2020-017027
[20]Bourcier R, Marnat G, Labreuche J, *et al.* Balloon Guide Catheter is Not Superior to Conventional Guide Catheter when Stent Retriever and Contact Aspiration are Combined for Stroke Treatment. *Neurosurg* 2021;**88**:E83–90. doi:10.1093/neuros/nyaa315
[21]Bourcier R, Saleme S, Labreuche J, *et al.* More than three passes of stent retriever is an independent predictor of parenchymal hematoma in acute ischemic stroke. *J NeuroIntervent Surg* 2019;**11**:625–9. doi:10.1136/neurintsurg-2018-014380
[22]Liebeskind DS, Saber H, Xiang B, *et al.* Collateral Circulation in Thrombectomy for Stroke After 6 to 24 Hours in the DAWN Trial. *Stroke* 2022;**53**:742–8. doi:10.1161/STROKEAHA.121.034471
[23]Anadani M, Finitsis S, Clarençon F, *et al.* Collateral status reperfusion and outcomes after endovascular therapy: insight from the Endovascular Treatment in Ischemic Stroke (ETIS) Registry. *J NeuroIntervent Surg* 2021;:neurintsurg-2021-017553. doi:10.1136/neurintsurg-2021-017553
[24]Anadani M, Januel A-C, Finitsis S, *et al.* Effect of intravenous thrombolysis before endovascular therapy on outcome according to collateral status: insight from the ETIS Registry. *J NeuroIntervent Surg* 2022;:neurintsurg-2021-018170. doi:10.1136/neurintsurg-2021-018170
[25]Jeanneret V, Yepes M. The Plasminogen Activation System Promotes Dendritic Spine Recovery and Improvement in Neurological Function After an Ischemic Stroke. *Transl Stroke Res* 2017;**8**:47–56. doi:10.1007/s12975-016-0454-x
[26]Xu H, Ping Y, Lin H, *et al.* Antiplatelet Strategies and Outcomes in Patients with Noncardioembolic Ischemic Stroke from a Real-World Study with a Five-Year Follow-Up. *Transl Stroke Res* 2017;**8**:228–33. doi:10.1007/s12975-016-0516-0
[27]Yao Z, Wang L, Wu X, *et al.* Enhanced Procoagulant Activity on Blood Cells after Acute Ischemic Stroke. *Transl Stroke Res* 2017;**8**:83–91. doi:10.1007/s12975-016-0501-7
[28]Fischer U, Kaesmacher J, Strbian D, *et al*. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet. 2022 Jul 9;400(10346):104-115. doi: 10.1016/S0140-6736(22)00537-2. PMID: 35810756.
[29]Hao Y, Yang D, Wang H, *et al.* Predictors for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of Acute Ischemic Stroke. *Stroke* 2017;**48**:1203–9. doi:10.1161/STROKEAHA.116.016368

[30]Broocks G, Kemmling A, Faizy T, et al. Effect of thrombectomy on oedema progression and clinical outcome in patients with a poor collateral profile. *Stroke and Vascular Neurology* 2021;6:doi: 10.1136/svn-2020-000570.

Fig.1. Flowchart of the study

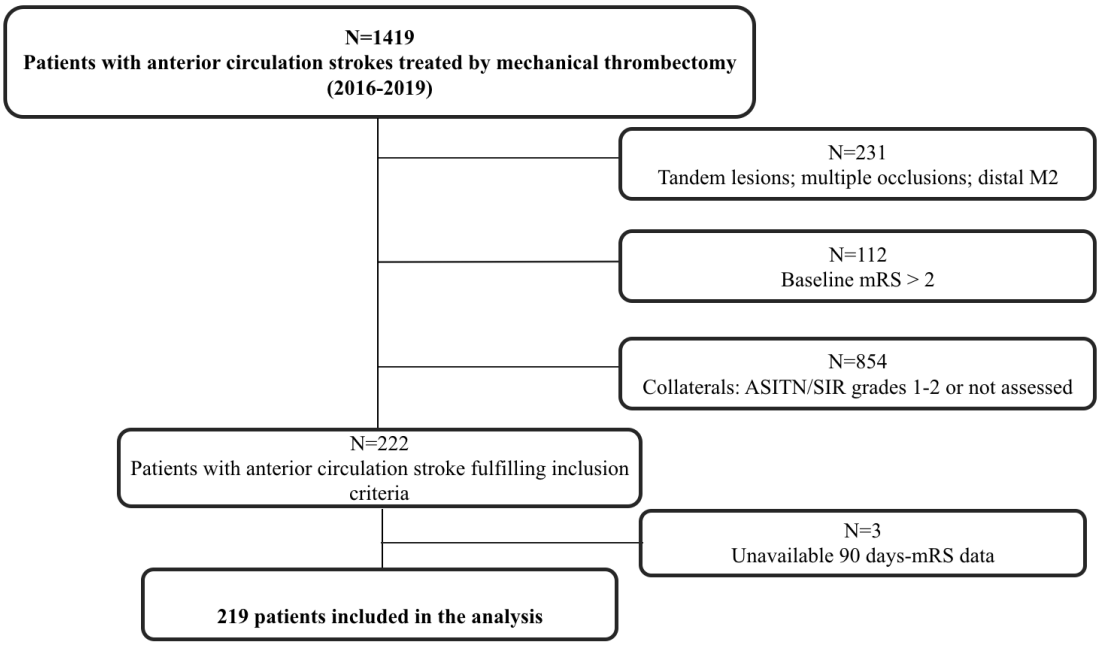


Table 1. Overall study population data and univariate analysis (primary endpoint).

	Overall *(N=219)*	Favorable outcome *(N=116)*	*Unfavorable outcome (N=103)*	*p*
Females, N(%)	117 (53.4)	56 (48)	46 (45)	0.59
Age, mean±SD	70.6 ±16	65.3 ±16.9	76.6 ±12.9	**<0.001**
Baseline mRS, N(%)				
0	181 (82)	105 (91)	76 (74)	
1	23 (10)	11 (9)	12 (12)	**<0.001**
2	15 (7)	0	15 (14)	
Baseline NIHSS, median (IQR)	15 (9-19.25)	12 (7-17)	18 (14-21)	**<0.001**
Occlusion site, N(%)				
ICA terminus	14 (6)	6 (5)	8 (8)	
M1-MCA	165 (74)	83 (72)	82 (79)	0.21

Proximal M2	40 (18)	27 (23)	13 (13)	
Side, N(%)				
Left	115 (53)	62 (53)	53 (51)	0.76
Right	104 (47)	54 (47)	50 (50)	
Baseline ASPECTS, median (IQR)	8 (7-9)	8 (7-9)	8 (7-9)	0.1
Secondary transfer, N(%)	132 (60)	63 (54)	69 (67)	0.06
Onset-to-groin, mean±SD	230.12±113.09	225.5 ±82.8	239.7 ±87.1	0.22
Onset-to-recanalization, mean±SD	288.3±117.3	270.4 ±93	299.4 ±96	**0.03**
Groin-to-recanalization, mean±SD	53.8±41.1	46.3 ±32.7	63.1 ±47.6	**0.004**
IVT, N(%)	116 (53)	72 (62)	44 (43)	**0.004**
Anesthesia protocol, N(%)				
General anesthesia	38 (17)	16 (14)	22 (21)	0.12
Conscious sedation	157 (72)	90 (78)	67 (65)	
Local anesthesia	24 (11)	10 (9)	14 (14)	
BGC used, N(%)	61 (28)	38 (33)	23 (22)	0.09
First-line strategy, N(%)				
Aspiration	137 (63)	69 (59)	68 (66)	0.08
Stent retriever/Combined	82 (37)	47 (41)	35 (34)	
First pass effect	89 (41)	50 (43)	39 (38)	0.43
N° of passes, mean±SD	2.3 ±2	2 ±1.3	2.7 ±2.5	**0.01**
mTICI, N(%)				
2b-3	194 (89)	109 (94)	85 (82)	**0.002**
2c-3	153 (70)	89 (77)	64 (62)	
Complications, N(%)	26 (12)	15 (13)	11 (11)	0.63
24h-NIHSS, median (IQR)	8 (3-17)	4 (2-8)	16.5 (11-20.75)	**<0.001**
24h-ASPECTS, median (IQR)	7 (6-8)	7 (5-8)	6 (3-8)	**<0.001**

PH1/PH2	30 (13.6)	10 (8.6)	20 (20)	**0.02**
sICH, N(%)	13 (6)	0	13 (13)	**<0.001**
Recurrent stroke, N(%)	11 (5)	3 (3)	8 (8)	0.09

BGC= balloon guiding catheter; ICA= internal carotid artery; IQR= interquartile range; IVT= intravenous thrombolysis; MCA= middle cerebral artery; mRS= modified Rankin Scale; SD=standard deviation; sICH= symptomatic intracerebral hemorrhage. PH1/PH2= parenchymal hemorrhage type 1 and 2 according to the ECASS-III classification.

Table 2 – Secondary endpoints.

	Recanalized patients (2b-3)			***Mortality***			***sICH****		
	Favorable outcome (mRS 0-2, N=110)	*Unfavorable outcome (mRS 3-6, N=84)*	*p*	*Survival (N=189)*	*Death (N=30)*	*p*	*No sICH (N=198)*	*sICH (N=13)*	*p*
Sex (female), N(%)	58 (53)	46 (55)	0.78	102 (54)	15 (50)	0.6	105 (54)	7 (54)	0.9
Age, mean ± SD	64.8 ±17.1	75.9 ±13.7	**<0.001**	68.9 ±16.5	81.2 ±8,0	**<0.001**	69.9 ±16.4	78.8 ±7,7	0.06
Baseline mRS, N(%)									
0	99 (90)	64 (76)		163 (86)	18 (60)		168 (84)	9 (70)	
1	11 (10)	7 (8)	**<0.001**	19 (10)	4 (13)	**<0.001**	20 (10)	2 (15)	0.13

2	0	13 (16)		7 (4)	8 (27)		12 (6)	2 (15)	
Baseline NIHSS, median (IQR)	12 (7-17)	18 (15-21)	**<0.001**	8 (15-19)	19 (14.5-21.5)	**0.002**	15 (9-19)	19 (15-21)	0.05
Occlusion site									
ICA Terminus	5 (4)	6 (7)		139 (74)	26 (86)		154 (77)	8 (61)	
M1-MCA	80 (73)	69 (82)	0.08	38 (20%)	2 (7%)	0.21	34 (17%)	4 (31%)	0.34
Proximal M2-MCA	25 (23)	9 (11)		12 (6%)	2 (7%)		12 (6%)	1 (8%)	
Side, N(%)									
Left	59 (54)	46 (55)	0.87	97 (51)	18 (60)	0.37	105 (53)	7 (54)	0.95
Right	51 (46)	38 (45)		92 (49)	12 (40)		93 (47)	6 (46)	
Baseline ASPECTS, median (IQR)	8 (7-9)	8 (7-9)	0.24	8 (7-9)	7 (7-8)	0.17	8 (7-9)	7 (5.75-8)	**0.03**
Secondary transfers, N(%)	59 (54)	58 (69)	**0.03**	115 (61)	17 (57)	0.66	119 (60)	8 (62)	1
Onset-to-groin, mean ± SD	218.7 ±71.6	234 ±80	0.18	233.5 ±88.1	223.7 ±62.6	0.83	233.2 ±87.3	218.2 ±64.6	0.63

Onset-to-recanalization, mean ± SD	263.8 ±80	287.1 ±91.8	0.07	283.1 ±97.8	286.7 ±77.6	0.53	282.2 ±97.9	300.8 ±64.3	0.14
Groin-to-recanalization, mean ± SD	45.1 ±32.2	52.7 ±39	0.16	51.7 ±37,8	69.0 ±56.5	0.35	51.8 ±39.5	82.5 ±51.3	**0.03**
IVT	70 (64)	38 (45)	**0.01**	106 (57)	10 (33)	**0.02**	108 (54)	4 (31)	0.1
Anesthesia protocol, N (%)									
General anesthesia	15 (14)	17 (20)		32 (17)	6 (20)		36 (18)	2 (15)	
Conscious sedation	85 (77)	56 (67)	0.26	136 (72)	21 (70)	0.91	142 (71)	9 (70)	0.81
Local anesthesia	10 (9)	11 (13)		21 (11)	3 (10)		22 (11)	2 (15)	
Use of BGC, N(%)	36 (33)	20 (24)	0.17	55 (29)	6 (20)	0.3	60 (30)	1 (8)	0.12
First-line strategy									
Aspiration	65 (59)	57 (68)		119 (63)	17 (59)		122 (61)	10 (77)	
Stent retriever/ Combined	45 (41)	27 (32)	0.08	70 (37)	12 (41)	0.07	77 (39)	3 (23)	0.51
First pass effect, N(%)	50 (45)	39 (46)	0.89	79 (42)	10 (33)	0.38	86 (43)	1 (8)	**0.01**

N° of passes, mean ± SD	1.9 ±1.3	2.2 ±1.6	0.11	2.2 ±1.6	3.0 ±3.6	0.36	2.3 ±2.0	3.5 ±2.0	**0.01**
mTICI									
0-2a	-	-		*17 (9)*	*8 (27)*		*20 (10)*	*5 (38)*	
			-			*0.01*			***0.01***
2b-3	-	-		*172 (91)*	*22 (73)*		*180 (90)*	*8 (62)*	
Complications, N(%)	15 (13)	11 (10)	0.63	22 (12)	4 (13)	0.9	23 (12)	3 (23)	0.2
*24h-NIHSS, median (IQR)***	4 (2-7)	16 (9.5-20)	**<0.001**	7 (2-14)	20 (16.75-24.25)	**<0.001**	7 (3-16)	20 (22-26)	**<0.001**
*24h-ASPECTS, median (IQR)***	8 (7-9)	6 (5-8)	**<0.001**	8 (7-9)	5 (3-6)	**<0.001**	7 (5-9)	5 (3-6)	**<0.001**
sICH, N(%)*	0	8 (10)	**<0.001**	8 (4)	5 (17)	**0.03**	-	-	-
*Stroke recurrence**, N(%)*	3 (3)	8 (10)	0.06	5 (3)	6 (21)	**0.001**	11 (6)	0	**0.001**

* Data available for 211/219 patients

** Data available for 204/219 patients

BGC= balloon guiding catheter; ICA= internal carotid artery; IQR= interquartile range; IVT= intravenous thrombolysis; MCA= middle cerebral artery; mRS= modified Rankin Scale; SD=standard deviation; sICH= symptomatic intracerebral hemorrhage.

Table 3. Multivariate analysis for primary and secondary endpoints

	P value	OR [IC 95%]
Primary endpoint - Unfavorable outcome in overall population		
Age	0.001	1,05 [1.02 - 1.09]
24h-NIHSS	<0.001	1.23 [1.14 - 1.32]
Secondary transfers	0.002	4.41 [1.70 - 11.43]
IVT	0.009	0.28 [0.11 - 0.73]
24h-ASPECTS	<0.001	2.42 [1.84 - 7.21]
Secondary endpoints		
	Unfavorable outcome in adequately recanalised patients (mTICI 2b-3)	
Age	0.0002	1.05 [1.03 - 1.08]
Baseline NIHSS	<.0001	1.15 [1.07 - 1.22]
IVT	0.022	0.41 [0.19 – 0.88]
Secondary transfers	0.005	2.95 [1.38 – 6.33]
	Mortality	
Baseline mRS *1 vs 0* *2 vs 0*	0.003 0.534 0.0006	 1.57 [0.38 – 6.47] 10.67 [2.78 – 41.02]
Baseline NIHSS	0.003	1.17 [1.05 - 1.27]
mTICI (2B-3)	0.012	0.18 [0.05 – 0.69]
	sICH	
Age	0.039	1.08 [1.07 - 1.29]
Baseline ASPECTS	0.005	0.53 [3.87 - 106.34]
First pass effect	0.033	0.10 [0.01 - 0.83]

Multivariate analysis adjusted for confounding factors (stroke recurrences). Only variables with significant differences are shown. IVT = intravenous thrombolysis. sICH=symptomatic hemorrhage, ECASS-PH1/PH2: European Cooperative Stroke Study/Parenchymal Hemorrhage type 1 and type 2. Adjusted for: Age, Side, Baseline ASPECTS, Baseline mRS, Baseline NIHSS, Occlusion site, Anesthesia protocol, OTR (onset to recanalization), Procedure time, IV

thrombolysis, First pass effect, Final mTICI, Number of passes, Complications, Secondary transfers, BGC used.

Supplemental Table 1. Subgroup analysis of patients with near-to-complete recanalization (final mTICI 2c-3, N= 153).

	mRS0-2 (N=91)	mRS3-6 (N=62)	***0.003***
Sex (female), N(%)	49 (53)	36 (58)	0.78
Age, mean ± SD	64.7 ±15.3	78.1 ±15.3	**<0.001**
Baseline mRS, N(%)			
0	82 (90)	49 (79)	
1	9 (10)	4 (6)	**<0.001**
2	0	9 (15)	
Baseline NIHSS, median (IQR)	14.5 (8.75-19)	19 (16-22.5)	**<0.001**
Occlusion site			
ICA Terminus	3 (3)	4 (6)	
M1-MCA	71 (78)	54 (87)	0.07
Proximal M2-MCA	17 (18)	4 (7)	
Side, N(%)			
Left	54 (59)	32 (52)	0.34
Right	37 (41)	30 (48)	
Baseline ASPECTS, median (IQR)	8 (7-8.5)	8 (7-9)	0.44
Secondary transfers, N(%)	50 (55)	43 (69)	0.07
Onset-to-groin, mean ± SD	221.9 ±79.4	226 ±76.8	0.43
Onset-to-recanalization, mean ± SD	260.8 ±77.1	271.5 ±85.6	0.19
Groin-to-recanalization, mean ± SD	39.2 ±30.2	45.3 ±31.2	0.39

IVT, N(%)	61 (67)	29 (47)	**0.01**
Anesthesia protocol, N (%)			
General anesthesia	13 (14)	12 (19)	
Conscious sedation	68 (75)	43 (70)	0.71
Local anesthesia	10 (11)	7 (11)	
Use of BGC, N(%)	32 (35)	19 (30)	0.33
First-line strategy			
Aspiration	53 (58)	40 (65)	0.43
Stent retriever/ Combined	38 (41)	22 (35)	
First pass effect, N(%)	48 (53)	37 (60)	0.39
N° of passes, mean ± SD	1.6±1.1	1.7 ±1.4	0.87
Complications, N(%)	9 (10)	4 (6)	0.18
*24h-NIHSS, median (IQR)***	4 (2-7.75)	17 (10-20)	**<0.001**
*24h-ASPECTS, median (IQR)***	8 (7-9)	6 (5-8)	**<0.001**
sICH, N(%)*	0	2 (3)	0.16
*Stroke recurrence**, N(%)*	3 (3)	8 (13)	0.05

mRS= modified Rankin Scale, SD= standard deviation, IQR=interquartile range, ICA= internal carotid artery, MCA= Middle cerebral artery, IVT= intravenous thrombolysis, BCG= ballon guiding catheter, sICH= symptomatic intracerebral hemorrhage

Supplemental Table 2. Subgroup analysis of good outcome according to the time elapsed between onset of symptoms and recanalization.

	OTR <6h (N=176)*	OTR >6h (N=32)**	
Sex (female), N(%)	93 (52)	18 (56)	0.72
Age, mean ± SD	70.3 ±16.6	72.8 ±12.1	0.38
Baseline mRS, N(%)			
0	145 (83)	28 (88)	
1	20 (11)	2 (6)	0.7
2	11 (6)	2 (6)	
Baseline NIHSS, median (IQR)	18 (15-21)	12 (6-16)	**0.004**
Occlusion site			
ICA Terminus	11 (6)	3 (9)	
M1-MCA	136 (78)	19 (59)	0.08
Proximal M2-MCA	29 (16)	10 (31)	
Side, N(%)			
Left	95 (54)	14 (44)	0.28
Right	81 (46)	18 (56)	
Baseline ASPECTS, median (IQR)	8 (7-9)	8 (7-8.5)	0.76
Secondary transfers, N(%)	100 (57)	24 (75)	0.053
Onset-to-groin, mean ± SD	206 ±51.4	388.1 ±69.2	**< 0.001**
Groin-to-recanalization, mean ± SD	46.7 ±34.2	95.6 ±81.4	**<0.001**
IVT, N(%)	101 (57)	11 (34)	**0.01**
Anesthesia protocol, N (%)			
General anesthesia	30 (17)	8 (25)	
Conscious sedation	127 (72)	21 (65)	0.55
Local anesthesia	19 (11)	3 (10)	

Use of BGC, N(%)	46 (26)	13 (40)	0.09
First-line strategy			
Aspiration	116 (66)	14 (44)	**0.02**
Stent retriever/ Combined	60 (34)	18 (56)	
First pass effect, N(%)	80 (45)	5 (15)	**0.001**
N° of passes, mean ± SD	2.14±1.2	3 ±1.8	**<0.001**
Final mTICI 2b-3, N(%)	165 (94)	24 (75)	**<0.001**
Final mTICI 2c-3, N(%)	135 (76)	15 (47)	**<0.001**
Complications, N(%)	22 (13)	4 (12)	1
*24h-NIHSS, median (IQR)***	16 (10-20)	11 (6-18.5)	**<0.001**
*24h-ASPECTS, median (IQR)***	6 (5-8)	7 (6-8)	0.07
sICH, N(%)*	11 (6)	2 (6)	0.9
Stroke recurrence, N(%)	9 (5)	1 (3)	0.89
mRS0-2, N(%)	99 (56)	14 (44)	0.19

* 3 patients not recanalized
** 8 patients not recanalized

mRS= modified Rankin Scale, SD= standard deviation, IQR=interquartile range, ICA= internal carotid artery, MCA= Middle cerebral artery, IVT= intravenous thrombolysis, BCG= ballon guiding catheter, sICH= symptomatic intracerebral hemorrhage

Supplemental Table 3. Subgroup analysis of recanalization rate according to the administration of intravenous thrombolysis.

	mTICI 0-2a	mTICI 2b-3	Tot.	P
IVT-	17 (16%)	87 (84%)	104	0.02
IVT+	8 (7%)	110 (93%)	118	

IVT - = no administration of intravenous thrombolysis.

The results of the UNCLOSE Study showed that even patients with good collaterals may not reach a favorable clinical outcome in terms, independently on the endovascular technique or the type of anesthesia used.

The overall results were partially similar to those reported in literature, while certain factors did not show the same results. Indeed, this was one of the first papers investigating this specific cohort of patients with good collaterals.
Nevertheless, we could observe poor clinical outcomes (mRS3-6) in 47% of the patients with good collaterals assessed through the ASITN/SIR score. Mortality rate was 13.6%.

The role of IV thrombolysis as a "protective" factor is in line with the current results reported by the recent trial SWIFT DIRECT, which showed that the association IVT+MT provided better clinical results than the MT alone (*Fischer U et al., 2022*). The interaction between IVT and collaterals will be discussed in the following chapter.

Furthermore, we could observe how patients successfully recanalized in late temporal windows (>6h) had the same rate of favorable clinical outcomes than those recanalized before 6h and these had also a better clinical evolution with lower 24h-NIHSS (11 vs 16, $p<0.001$).

These results are in line with the so-called « ***late window paradox*** » (*Albers GW, 2018*), which explains how those patients treated in late windows are more selected through perfusional imaging in order to justify late treatments. For this reason, patients treated in late windows are associated with favorable outcomes, as it appeared in our cohort.

These data are particular interesting if we consider that:
- this cohort is considered to be the most likely to achieve functional independence after MT
- these clinical results were independent from the type of endovascular technique or from the type of anesthesia used.

Nevertheless, if we had already observed that the endovascular technique seems not to have a direct impact on clinical outcome (*Lapergue et al., 2017; Turk AS 3rd et al., 2019*), controversial results were published concerning the type of anesthesia and, in particular, a potential detrimental effect of general anesthesia on the collateral status (*Fandler-Höfler S et al., 2020; Raychev R et al., 2020*).

Although some Authors underlined the risk of a pressure drop in CC at the moment of the induction of the general anesthesia, it seems that the effect of general anesthesia could be more effective on poor collaterals, which would be more vulnerable than the good ones (*Liu D et al., 2021*).

Interestingly, the First Pass Effect was not significantly associated with a good clinical outcome, except for sICH. However, the hypothesis that CC could provide from one hand a higher resistance to ischemia also after the first manoeuver seems not to be supported.

Indeed, we have observed that longer procedures with a higher number of passes were associated with unfavorable outcomes.

These results could raise some questions concerning the assessment and the prognostic value of the CC in patients with AIS.

Indeed, although the ASITN/SIR scale is probably the most used classification to assess the CC in AIS, the inter- and intra-observer reliability between different operators is quite poor (*Ben Hassen W et al., 2019*). Therefore, there is a growing need for a tool that could help the assessment of CC in a reliable and easy way.

On the other hand, one could argue that collaterals that are judged as good or excellent basing on the ASINT/SIR scale, could be ineffective.

Future perspectives

The CC represents a potential tool for patients' selection and prediction of clinical outcome and hemorrhagic risk for patients treated by MT for AIS.

Although CC has already widely proven to play a central role, together with the recanalization grade, in determining favorable clinical outcomes and providing useful prognostic information about hemorrhagic transformation, it is not rare to observe a sort of "mismatch" between the CC status and the final clinical result.

Nevertheless, as we observed in the literature, the current grading scale to assess CC seems not to provide a reliable evaluation which is very subjective according to the observers. It is also possible that a different type of analysis, bases on solid physiopathological assumption, could improve the reliability of the currently most used angiographic scale: the ASITN/SIR.

This issue will be addressed in the next chapter, focusing on the critical analysis of the angiographic assessment of the CC.

4. CRITICAL ANALYSIS OF COLLATERALS ACCORDING TO DIGITAL SUBTRACTION ANGIOGRAPHY

In Chapter 3 the role of CC as a predictor of good clinical outcome for patients treated by MT for AIS secondary to LVOs was analyzed. Although the results is not significant, currently, the CC is considered as a relevant factor in determining the functional independence in AIS patients and it is considered as a co-factor together with the recanalization grade (mTICI score).

Indeed, as discussed in the previous chapters, the main role of CC is to modulate the evolution of the ischemic process, by providing a sort of "hemodynamic reserve" in case of arterial occlusion. However, patients with good collaterals can also be associated with unfavorable outcome or, at least, not reach a functional independence.

Therefore, even those patients who are considered the best candidates to MT with the current criteria could not benefit from the endovascular treatment and in particular those with older age, without administration of IVT and treated with long procedure times (*Consoli A et al., 2022 UNCLOSE*).

The CAPRI Study (*Consoli A et al., 2016*), reported in Chapter 2, had shown how the CC assessed thought the CCS was significantly associated with the CBV assessed on the CT Perfusion imaging. However, CCS is just one of the different classifications that have been proposed in order to assess the CC (*McVerry F et al., 2012*). More than 40 classifications have been proposed and about 20 are used in AIS patients.

The most used grading scale is the ASITN/SIR classification which describes a 5-grades scale for the assessment of collateral circulation (**Table 3**), based on an integrated semi-quantitative and qualitative evaluation of CC.

The different grades are calculated based on the peripheral or complete filling of the infarcted territory associated with the mention "rapid" or "slow" according to the difference of filling of the CC compared to the washout of the ACA (*Higashida RT et al., 2003*).

Table 3. *The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral grade*

ASITN/SIR Collateral grade	Definition
0	No collaterals visible to ischemic site
1	Slow collaterals to the periphery of ischemic site, with persistence of some of the defect, and to only a portion of the ischemic territory
2	Rapid collaterals to the periphery of ischemic site, with persistence of some of the defect, and to only a portion of the ischemic territory
3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde reprfusion

However, this classification presents some limitations. In particular, the assessment "per definition" of CC using ASITN/SIR is time-consuming and not easy-to-use. Moreover, the reported inter-observer agreement between different operators in the assessment of the ASITN/SIR score was far from being considered excellent (*Ben Hassen W et al., 2019*).

The subgroup of patients with good collaterals and unfavorable outcomes and the subjectivity of the assessment of CC could raise up some points of debate. In particular: **are good collaterals always effective?** This research question represented the aim of the following paper published in the *Journal of NeuroInterventional Surgery*.

Original research

Angiographic collateral venous phase: a novel landmark for leptomeningeal collaterals evaluation in acute ischemic stroke

Arturo Consoli ,[1,2] Silvia Pizzuto,[1] Alessandro Sgreccia ,[1] Federico Di Maria,[1] Oguzhan Coskun,[1] Georges Rodesch,[1] Bertrand Lapergue,[3] Jacques Felblinger,[2,4] Bailiang Chen,[2,4] Serge Bracard[4,5]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnis-2022-019653).

[1]Department of Diagnostic and Interventional Neuroradiology, Versailles Saint-Quentin en Yvelines University, Hôpital Foch, Suresnes, France
[2]CIC, Innovation Technologique, Université de Lorraine, INSERM, Nancy, France
[3]Department of Neurology, Versailles Saint-Quentin en Yvelines University, Hôpital Foch, Suresnes, France
[4]IADI, Université de Lorraine, INSERM, Nancy, France
[5]Department of Diagnostic and Therapeutic Neuroradiology, Université de Lorraine, Nancy University Hospital, Nancy Regional University Hospital Center, Nancy, France

Correspondence to
Dr Arturo Consoli, Department of Diagnostic and Interventional Neuroradiology, Versailles Saint-Quentin en Yvelines University, Hôpital Foch, Suresnes 92150, France; onemed21@gmail.com

Received 19 September 2022
Accepted 9 December 2022

To cite: Consoli A, Pizzuto S, Sgreccia A, *et al*. *J NeuroInterv Surg* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnis-2022-019653

ABSTRACT

Background Although recanalization rates constantly increase (>80%), a favorable clinical outcome is achieved in only 45–55% of patients undergoing mechanical thrombectomy (MT) for anterior circulation stroke. Collateral circulation seems to play a major role in determining this discrepancy. The aim of the study was to investigate a novel angiographic landmark assessing the collateral venous phase (CVP) compared with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) score, based on the arterial collateral assessment.

Methods Two hundred patients with anterior circulation stroke treated by MT between 2016 and 2021 were included. The ASITN/SIR score and the presence of CVP were blindly evaluated by expert neuroradiologists. Three subanalyses were performed comparing patients with good versus poor collaterals, CVP presence versus absence, and a composite analysis including both ASITN/SIR and CVP grading results.

Results Good collateral circulation (ASITN >2) was observed in 113 patients (56.5%) whereas CVP was present in 90 patients (45%) and mostly in patients with good collaterals. Favorable clinical and neuroradiological outcomes were more likely observed in patients with both good collaterals and the presence of CVP than in those with good collaterals and absence of CVP (modified Rankin Scale score 0–2: 77.3% vs 7.9%, p<0.0001; mortality: 9.3% vs 26.3%, p=0.02; 24-hour Alberta Stroke Program Early CT Score: 8 vs 6, p<0.0001), while ASITN/SIR score alone was not significantly associated with clinical outcomes.

Conclusions The presence of CVP improves the angiographic assessment of collateral circulation. CVP could be proposed as a new imaging landmark to better understand the functionality of collaterals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although the impact of collaterals in the physiopathology of acute ischemic stroke is a known matter of investigation, their hemodynamic features are poorly known. Growing attention is being paid to the venous profile of collaterals.

WHAT THIS STUDY ADDS

⇒ This study provides an analysis of a new potential landmark of the effectiveness of collateral vessels: the presence of the collateral venous phase directly on digital subtraction angiography.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The assessment of the collateral venous phase could drive the therapeutic management of patients with acute ischemic stroke by adding new physiopathological data about the potential evolution of the ischemic lesion.

INTRODUCTION

Although mechanical thrombectomy (MT) has significantly changed the approach to the management of acute ischemic stroke, a large number of patients still do not reach functional independence after endovascular treatment. Indeed, a favorable clinical outcome is not achieved in about 45–55% of patients with adequate recanalization.[1 2] Several studies have focused on the issue of patient selection with multimodal CT/MRI and collateral scores without achieving a general consensus.[3 4] In this context, the role of the collateral circulation has been widely investigated during the last decade and its correlation with non-invasive multimodal neuroimaging as well as the impact on clinical outcome has been largely reported in the literature.[5 6] Furthermore, there is a growing interest in the venous phase of the collateral circulation, which is not considered in the currently available grading scales.[7 8]

The aim of this study was to introduce the novel concept of the angiographic assessment of the collateral venous phase (CVP) as a prognostic factor and a potential selection tool for patients with anterior circulation large vessel occlusion (LVO) undergoing MT. A comparative analysis of clinical and neuroradiological outcomes was performed in patients assessed using a novel dichotomous landmark to evaluate the venous phase of the collateral circulation (present vs absent) and the conventional grading scale American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR)

score,[9] which provides an assessment of the collateral circulation (poor vs good) based on the evaluation of its arterial filling. According to our hypothesis, the presence of the CVP and good collaterals would be a stronger predictor of favorable clinico-neuroradiological outcomes compared with the absence of the CVP and with the standalone ASITN/SIR assessment.

METHODS

This is a retrospective single-center analysis based on a prospective web-based registry (ETIS Registry NCT03776877). Patients with LVOs (M1, internal carotid artery (ICA) terminus ± extracranial ICA occlusion) of the anterior circulation treated by MT from January 2016 and December 2021 and meeting the quality inclusion criteria were included. The study received the approval of the local Institutional Review Board waiver for informed consent.

Quality inclusion criteria

Two expert interventional neuroradiologists with >15 years' experience who were not involved in the procedures were responsible for the Quality Control core laboratory and performed a double-blind assessment of the pretreatment DSA data. The Quality Control core laboratory evaluated the eligibility for patient inclusion, the grade of collateral circulation, and the presence/absence of the CVP (CVP+ or CVP−). Patients were considered eligible for inclusion according to specific quality requirements: (1) angiograms with a late venous phase defined as a complete washout of the superior longitudinal sinus; (2) the absence of motion artifacts which could bias the collateral evaluation; (3) the presence of contralateral carotid injection with late venous phase in case of tandem occlusions. A flow chart of the study is provided in online supplemental file 1.

Evaluation of the collateral circulation

The grade of collateral circulation was assessed on both anteroposterior (AP) and lateral projections using the ASITN/SIR grading and good collaterals were defined as ASITN/SIR grade >2. The CVP was defined as the presence of the subcortical veins in the region of the collateral circulation (see figure 1 and online supplemental video 1). These veins are visible in the AP projection as perpendicular centrifugal veins draining the subcortical and cortical territory in the vascular region of the occluded artery and are tributaries of the cortical veins draining in the superior sagittal sinus or the transverse sinus. Therefore, the evaluation of CVP was performed on the AP projection of the pretreatment DSA. For both ASITN/SIR (single grade and dichotomous poor vs good) grade and presence/absence of the collateral venous, phase k interobserver agreement was calculated.

Clinical and neuroradiological data

Demographics (age, sex, and risk factors), clinical data, and outcomes (baseline and 24-hour National Institutes of Health Stroke Scale (NIHSS) score, 3-month modified Rankin Scale (mRS) score and time metrics were prospectively collected in the ETIS Registry by certified neurologists. Diagnostic (baseline and 24-hour Alberta Stroke Program Early CT Score (ASPECTS), European Cooperative Acute Stroke Study (ECASS III) scale for symptomatic intracerebral hemorrhage (sICH)), and procedural data and outcomes such as first-line technique, modified Thrombolysis in Cerebral Infarction score (mTICI), first pass effect (FPE), and final mTICI were prospectively collected in the ETIS Registry by an expert neuroradiologist. A good clinical outcome was defined as 3-month mRS score of 0–2 and successful recanalization as mTICI 2b–3, whereas favorable neuroradiological outcomes were defined according

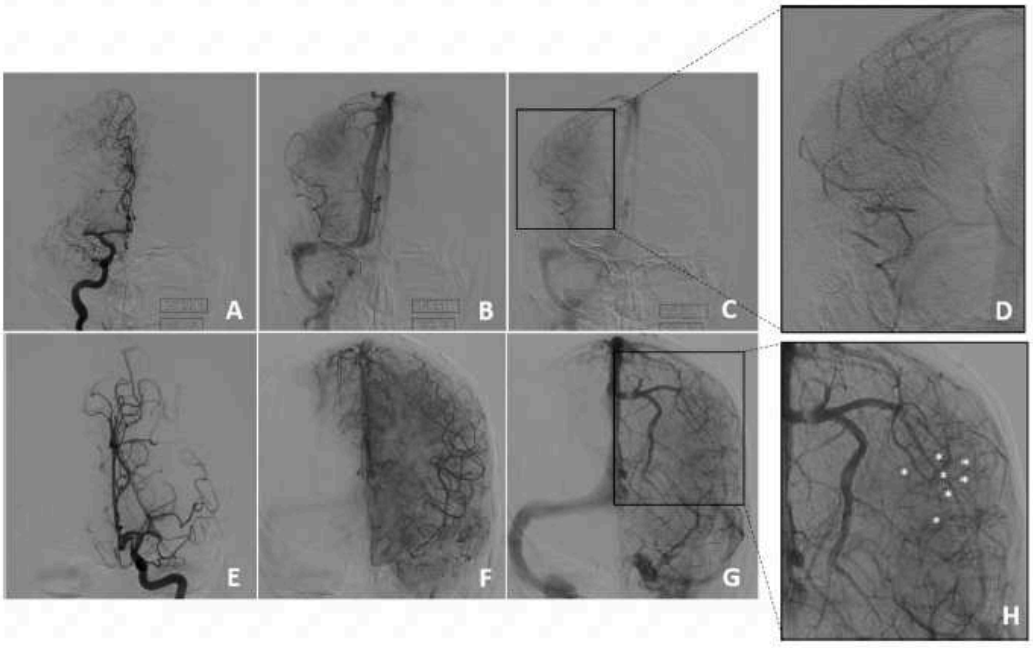


Figure 1 Anteroposterior DSA projections in two patients with middle cerebral artery (MCA) M1 occlusion and ASITN/SIR grade 4 collateral circulation. (A) Arterial, (B) parenchymal and (C) late venous phase in a patient with a right M1-MCA occlusion. (D) Magnification of the collateral region showing the absence of the collateral venous phase (CVP−). (E) Arterial, (F) parenchymal and (G) late venous phase in a patient with a left M1-MCA occlusion. (H) Magnification of the collateral venous region showing the presence of the collateral venous phase (CVP+). CVP is highlighted by white asterisks showing the collateral veins, which are visible as perpendicular subcortical venous structures.

to the 24-hour ASPECTS and the absence of hemorrhagic transformation.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as mean (SD) or median (IQR) for non-normal distribution. Normality of distributions was assessed graphically using the Shapiro–Wilk test. Three subanalyses were performed comparing patients' outcomes according to the ASITN/SIR score alone, CVP alone, and their interaction. Baseline characteristics were compared according to the ASITN/SIR score and CVP+/− using the χ^2 or Fisher's exact tests for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables as appropriate. Tukey tests were used for multiple comparisons. The Kruskal–Wallis test was used to assess the interaction between good/bad collateral circulation and CVP+/− in relation to clinical and neuroradiological outcomes. Multivariate analysis was performed to look for risk factors. The final models were presented using backward elimination. All tests were bilateral with a 5% degree of significance. Statistical analysis was performed with the SAS 9.4 software.

RESULTS

Two hundred patients of mean age 65.8±17.3 years (45% women) were included in the study according to the inclusion criteria (see online supplemental figure 1). Overall results are summarized in table 1.

A good collateral circulation (ASITN/SIR grade >2) was observed in 113 patients (56.5%) whereas CVP+ was observed in 90 patients (45%). Kappa interobserver agreement was 0.95 for ASITN/SIR score dichotomization (>2 vs <2), 0.60 for the single ASITN/SIR grades, and 0.89 for the CVP assessment. Adequate recanalization (mTICI 2b–3) was achieved in 82% of patients and FPE (mTICI 2b–3) was observed in 40%. A favorable clinical outcome was achieved in 96 patients (48%) and mortality was 19.5%. Subgroup analysis of patients with good and poor collateral scores according to the ASITN scale and that performed according to the CVP+/− are reported in table 2.

According to the composite assessment, among the 87 patients with poor collaterals, we observed better clinical and neuroradiological outcomes in patients with a concomitant CVP+ than in those with CVP− (table 3). Considering patients with good collaterals, those with CVP+ had lower baseline NIHSS compared with those with CVP− (12 vs 17, p=0.0004), higher median baseline (8 vs 7, p=0.007) and 24-hour ASPECTS (8 vs 5, p<0.0001), higher rates of favorable clinical outcome (mRS 0–2: 77.3% vs 7.9%, p<0.0001), lower mortality (9.3% vs 26.3%, p=0.02), sICH (1.5% vs 16.2%), and intraparenchymal hematoma (10.3% vs 35.1%, p=0.002). Statistical data are shown in table 3.

DISCUSSION

The issue of futile reperfusions has been investigated in the literature.[1 10] A possible interpretation of this phenomenon could be related to the difference that exists between the concept of recanalization and reperfusion. Indeed, recanalization represents the anatomical result which follows the removal of the clot from the occluded artery, whereas reperfusion could be interpreted as the biological effect of flow restoration on the brain tissue. Based on this assumption, the recanalization of an occluded artery can determine the recovery of brain areas where the perfusion was maintained during the occlusion because of the presence of a

Table 1 Overall characteristics of the study population

Characteristics	N=200
Baseline characteristics	
Age, mean±SD	65.9±15.9
Women, n (%)	89 (44.5%)
Risk factors, n (%)	
Hypertension	98 (50%)
Diabetes	22 (11.5%)
Smoking	43 (24.9%)
Atrial fibrillation	31 (17.9%)
Previous stroke	32 (16.4%)
Dyslipidemia	68 (36.2%)
Anti-thrombotic treatments	71 (35.9%)
Baseline NIHSS, median (IQR)	15.9 (12–20)
Imaging method, n (%)	
MRI	177 (88.5%)
CT scan	23 (11.5%)
IV thrombolysis, n (%)	91 (45.5%)
Time metrics (min)	
Onset-to-imaging, mean±SD	158.4±201.4
Median (Q1– 3) (IQR)	109 (82.5–156) (73.5)
Onset-to-groin, mean±SD	281.1±219.4
Median (Q1–Q3) (IQR)	229 (178.5–305) (126.5)
Onset-to-recanalization±SD	351.2±248.6
Median (Q1–Q3) (IQR)	290(229–388) (159)
Procedural data and outcomes	
ASITN >2, n (%)	113 (56.5%)
CVP+, n (%)	90 (45.0%)
Occlusion site, n (%)	
MCA	148 (74.0%)
ICA siphon	26 (13.0%)
Tandem	26 (13.0%)
Type of anesthesia, n (%)	
General anesthesia	44 (22.0%)
Conscious sedation	149 (74.5%)
Local anesthesia	7 (3.5%)
MT first-line technique, n (%)	
SR or combined	171 (85.5%)
CA	29 (14.5%)
First pass effect 2c–3, n (%)	62 (31%)
First pass effect 2b–3, n (%)	79 (39.5%)
Final mTICI 2c–3, n (%)	122 (61%)
Final mTICI 2b–3, n (%)	164 (82%)
Number of passes, mean±SD	2.6±2.0
Complications, n (%)	11 (5.5%)
Clinical and neuroradiological outcomes	
sICH, n (%)	19 (10.2%)
PH1/PH2, n (%)	36 (20.0%)
mRS 0–2, n (%)	96 (48.0%)
Mortality, n (%)	39 (19.5%)

CA, contact aspiration; CVP+, presence of collateral venous phase; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; PH1/PH2, parenchymal hematoma according to the ECASS III scale; sICH, symptomatic intracerebral hemorrhage; SR, stent-like retriever.

Table 2 Subgroup analysis according to the ASITN grade and the CVP

	ASITN			CVP		
	ASITN >2	ASITN 0–2	P value	CVP+	CVP–	P value
No of patients	113	87		90	110	
Age, mean±SD	65.8±16.9	65.9±14.6	0.98	65.1±18.0	66.4±14.1	0.56
Baseline NIHSS, median (IQR)	16 (11–19)	18 (13–22)	0.01	14,5 (10–19)	17,5 (14–21)	0.0006
Baseline ASPECTS, median (IQR)	8 (7–8)	6 (4–7)	<0.0001	8 (7–8)	6 (4–8)	<0.0001
General anesthesia, n (%)	25 (22.1%)	19 (21.8%)	0.96	22 (24.4%)	22 (20.0%)	0.45
CVP+	75 (66.3%)	15 (17.2%)	<0.0001			
Good collaterals (ASITN >2)				75 (83.3%)	38 (34.5%)	<0.0001
Occlusion site, n (%)						
MCA	92 (81.5%)	56 (64.4%)	0.007	78 (86.6%)	70 (63.6%)	0.001
ICA siphon	10 (8.8%)	16 (18.4%)		6 (6.7%)	20 (18,2%)	
Tandem	11 (9.7%)	15 (17.2%)		6 (6.7%)	20 (18.2%)	
Risk factors, n (%)						
Hypertension	49 (44.9)	49 (56.3)	0.11	38 (43.2%)	60 (55.6%)	0.08
Diabetes	12 (11.2)	10 (11.8)	0.91	7 (8.0%)	15 (14.4%)	0.16
Smoking	21 (21.0)	22 (30.1)	0.17	19 (24.0%)	24 (25.5%)	0.82
Atrial fibrillation	18 (18.0)	13 (17.8)	0.97	13 (16.9%)	18 (18.8%)	0.75
Previous stroke	19 (17.6)	13 (14.9)	0.62	12 (13.6%)	20 (18.7%)	0.34
Dyslipidemia	34 (32.4)	34 (41.0)	0.22	27 (31.4%)	41 (40.2%)	0.21
Anti-thrombotic therapies	42 (37.8)	29 (33.3)	0.51	30 (34.1%)	41 (37.3%)	0.64
IV thrombolysis, n (%)	51 (45.1)	40 (46.0)	0.91	47 (52.2%)	44 (40.0%)	0.08
FPE mTICI 2b–3, n (%)	51 (45.1%)	28 (32.2%)	0.06	45 (50.0%)	34 (30.9%)	0.006
FPE mTICI 2c–3, n (%)	40 (35.4%)	22 (25.3%)	0.13	35 (38.9%)	27 (24.5%)	0.029
Final mTICI 2c–3	74 (65.5%)	48 (55.2%)	0.14	65 (72.2%)	57 (51.8%)	0.003
Final mTICI 2b–3	93 (82.3%)	71 (81.6%)	0.90	79 (87.8%)	85 (77.3%)	0.054
Onset-to-imaging (min), mean±SD	167.6±220.2	146.6±174.6	0.45	154.9±193.1	161.4±208.8	0.82
<90	35 (31.0%)	29 (33.3%)	0.57	27 (30.0%)	37 (33.6%)	0.46
90–180	53 (46.9%)	44 (50.6%)		42 (46.7%)	55 (50.0%)	
≥180	25 (22.1%)	14 (16.1%)		21 (23.3%)	18 (16.4%)	
Onset-to-groin (min), mean±SD	292.0±237.1	266.9±194.5	0.42	261.3±202.6	297.3±231.9	0.24
<180	25 (22.1%)	25 (28.7%)	0.52	27 (30.0%)	23 (20.9%)	0.14
180–360	70 (62.0%)	51 (58.6%)		54 (60.0%)	67 (60.9%)	
>360	18 (15.9%)	11 (12.7%)		9 (10.0%)	20 (18.2%)	
Onset-to-recanalization, mean±SD	354.6±252.9	346.7±244.2	0.82	374.4±264.4	322.8±226.0	0.14
<4.5 hours	45 (39.8%)	36 (41.4%)	0.98	42 (46.7%)	39 (35.4%)	0.073
4.5–6 hours	32 (28.3%)	24 (27.6%)		27 (30.0%)	29 (26.4%)	
>6 hours	36 (31.9%)	27 (31.0%)		21 (23.3%)	42 (38.2%)	
Complications	5	6	0.8	5	6	0.8
24 hour-ASPECTS, median (IQR)	7 (5–8)	5 (3–7)	<0.0001	8 (6–8)	5 (3–7)	<0.0001
mRS 0–2, n (%)	61 (54.0%)	35 (40.2%)	0.054	69 (76.7%)	27 (24.5%)	<0.0001
Mortality, n (%)	17 (15.0%)	22 (25.3%)	0.070	7 (7.8%)	32 (29.1%)	<0.0001
sICH, n (%)	7 (6.7%)	12 (14.8%)	0.069	2 (2.4%)	17 (16.3%)	0.002
PH1/PH2, n (%)	20 (19.0%)	16 (21.3%)	0.705	7 (8.5%)	29 (29.6%)	0.0004
No of passes, mean±SD	2.39±1.92	2.89±2.14	0.086	1.99±1.38	3.11±2.32	<0.0001

ASITN, American Society of Interventional and Therapeutic Neuroradiology; ASPECTS, Alberta Stroke Program Early CT Score; CVP+, presence of collateral venous phase; FPE, first pass effect; mRS, modified Rankin Scale; PH1/PH2, parenchymal hematoma according to the ECASS III scale; sICH, symptomatic intracerebral hemorrhage.

functional collateral circulation. We have analyzed the potential impact of the CVP in predicting a good clinical outcome and mortality compared with and in association with the ASITN/SIR grade of collateral circulation.

Collateral ASITN/SIR-based analysis

The physiopathological concept that a good collateral circulation maintains cerebral perfusion during arterial occlusion would reflect the inverse relation between good collateral scores and

Table 3 Composite assessment of ASITN+CVP

	ASITN ≤2		ASITN >2		
	CVP−	CVP+	CVP−	CVP+	P value
No of patients	72	15	38	75	
Age, mean±SD	65.7±13.7	66.8±18.9	67.9±14.7	64.8±17.9	0.80
	0.59		0.47		
Baseline NIHSS, median (IQR)	18 (13–22)	19 (15–22)	17 (15–21)	12 (9–18)	0.0003
	0.61		0.0004		
Baseline ASPECTS, median (IQR)	6 (4–7)	7 (5–8)	7 (5–8)	8 (7–9)	<0.0001
	0.13		0.007		
General anesthesia, N(%)	15 (20.8%)	4 (26.7%)	7 (18.4%)	18 (24.0%)	0.87
	0.73		0.50		
Occlusion site					
MCA	42 (58.3)	14 (93.3)	28 (73.7)	64 (85.3)	0.006
ICA siphon	16 (22.2)	0 (0)	4 (10.5)	6 (8.0)	
Tandem	14 (19.5)	1 (6.7)	6 (15.8)	5 (6.7)	
	0.02		0.27		
FPE mTICI 2b–3, (%)	22 (30.6%)	6 (40.0%)	12 (31.6%)	39 (52.0%)	0.04
	0.55		0.04		
FPE mTICI 2c–3, n (%)	17 (23.6%)	5 (33.3%)	10 (26.3%)	30 (40.0%)	0.16
	0.52		0.15		
Final mTICI 2–3, n (%)	37 (51.4%)	11 (73.3%)	20 (52.6%)	54 (72.0%)	0.03
	0.12		0.04		
Final mTICI 2b–3, n (%)	58 (80.6%)	13 (86.7%)	27 (71.0%)	66 (88.0%)	0.16
	0.73		0.03		
Onset to recanalization, mean±SD	365.4±262.5	257.1±81.1	391.6±270.7	335.9±243.1	0.06
	0.02		0.06		
<4.5 hours	26 (36.1)	10 (66.7)	13 (34.2)	32 (42.7)	0.02
4.5–6 hours	22 (30.6)	2 (13.3)	7 (18.4)	25 (33.3)	
>6 hours	24 (33.3)	3 (20.0)	18 (47.4)	18 (24.0)	
	0.11		0.03		
24-hour ASPECTS, median (IQR)	5 (2–7)	7 (5–8)	5 (3–7)	8 (6–8)	<0.0001
	0.02		<0.0001		
mRS 0–2, n (%)	24 (33.3%)	11 (73.3%)	3 (7.9%)	58 (77.3%)	<0.0001
	0.004		<0.0001		
Mortality, n (%)	22 (30.6%)	0 (0%)	10 (26.3%)	7 (9.3%)	<0.0001
	0.01		0.02		
sICH, (%)	11 (16.4%)	1 (7.1%)	6 (16.2%)	1 (1.5%)	0.007
	0.68		0.01		
PH1/PH2, n (%)	16 (26.2%)	0 (0%)	13 (35.1%)	7 (10.3%)	0.002
	0.03		0.002		
No of passes, mean±SD	3.06±2.24	2.07±1.28	3.21±2.48	1.97±1.40	0.003
	0.10		0.02		

ASITN, American Society of Interventional and Therapeutic Neuroradiology; CVP+, presence of collateral venous phase; FPE, first pass effect; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH1/PH2, parenchymal hematoma according to the ECASS III scale; sICH, symptomatic intracerebral hemorrhage.

NIHSS as well as the proportional relation with the ASPECTS assessed on non-contrast CT, CT perfusion, diffusion-weighted imaging, and perfusion-weighted imaging.[11–13]

In our cohort, patients with good collaterals had a lower NIHSS score and higher ASPECTS than patients with poor collaterals (table 2). Furthermore, in this subanalysis, despite the fact that no significant difference was observed in terms of age, adequate recanalization and onset-to-recanalization time, patients with good collaterals had higher ASPECTS at 24-hour imaging. Among patients with good collaterals we found higher rates of favorable clinical outcomes (54% vs 40.2%) and lower rates of mortality (15% vs 25.3%), sICH (6.7% vs 14.8%), and

intraparenchymal hematoma (19% vs 23%), although a statistically significant result was not observed. These results are globally in line with those reported in the literature.[14–16]

CVP-based analysis

The results observed in this subanalysis were similar to those reported in the previous one. The favorable clinical and neuroradiological outcomes were strongly associated with the presence of a CVP (table 2), despite no significant difference being observed in terms of recanalization rate. These results could be partially explained by a higher rate of FPE in patients with CVP+ and a higher frequency of tandem occlusions in patients with CVP−. Furthermore, in patients with CVP+, a higher rate of mTICI 2c–3 was obtained. A meta-analysis by Kaesmacher *et al*[17] showed that the main factor influencing futile reperfusion was the achievement of mTICI 3 rather than mTICI 2b, whereas the inhomogeneity of the design of the included studies limited the interpretation of other factors. The authors concluded that the strategy to improve TICI 2b to TICI 2c–3 remains a matter of debate needing a prospective evaluation, although a potential benefit was reported in the literature.[18 19] Although the presence of CVP was not significantly time-dependent according to the onset-to-groin and onset-to-recanalization times, we observed in the multivariate analysis a lower rate of CVP+ in patients with an imaging-to-groin time >90 min (p=0.03), which could support the concept of a progressive deterioration in the venous permeability of the collateral circulation over time (see online supplemental tables 1A,1B). Interestingly, the other factors that were independently associated with CVP+ were IV thrombolysis and good collateral circulation, suggesting a potential role of thrombolysis in maintaining the patency of the microcirculation.

Combined ASITN-CVP analysis

The subanalysis of the composite assessment of the ASITN grade and the CVP provided significant results when CVP+ was associated with the ASITN evaluation. Patients with poor collaterals and CVP+ had better clinical and neuroradiological outcomes than those with CVP−, although these were recanalized significantly earlier (table 3). Interestingly, the most remarkable results were observed in the subgroup of patients with good collaterals. Although no difference in terms of recanalization grade, FPE rate, and onset-to-recanalization time was observed between patients with good and poor collaterals (table 2), patients with good collaterals had both a significantly better baseline profile and clinical and neuroradiological outcomes if CVP was present (table 3). Moreover, in patients with good collaterals and CVP+, we observed higher recanalization rates (mTICI 2b–3/2c–3), FPE, and a shorter onset-to-recanalization interval. These data could also be interpreted as the effect of good collaterals in influencing successful reperfusion, reducing the number of maneuvers, and increasing the chance of achieving a FPE, which has already been reported in the literature.[14 20 21]

Potential role of CVP

Although the concept of collaterals as a 'hemodynamic reserve' for the brain tissue remains a solid theory, we proposed a distinction concerning the extension of the collateral circulation and its functionality. As mentioned above, more than half of the patients treated by MT do not reach functional independence the endovascular treatment, even those with a good collateral circulation.[1 2] Tong *et al*[7] introduced the analysis of the venous collaterals, arguing that impairment of the venous outflow of collaterals could play a central role in their functionality. Indeed, the authors emphasized that venous and venules of the microcirculation could be responsible for the clearance of microemboli in the capillaries and venules of the microcirculation, generating a blood stasis in the collateral vessels and their involvement in the no-reflow phenomenon. Furthermore, the venous collaterals seem to play a major role in the maintenance of the cerebral blood volume during ischemia.[22]

The findings reported in the subanalysis of the composite assessment ASITN/SIR-CVP could support the concept that to evaluate only the extension of the collateral circulation may not be sufficient to properly assess the perfusional status of the brain. Indeed, when we consider that most of the patients with CVP+ are those with ASITN/SIR grades >2 (table 2), it is possible to assume that the CVP could help to differentiate patients with good but ineffective collaterals from those with good and effective collaterals. As shown in table 3, when we consider only patients with ASITN/SIR collaterals grades >2, the difference in terms of favorable clinical outcome was strongly significant and more likely in patients with CVP+ (p<0.0001). Furthermore, the multivariate analysis (see online supplemental table 1C) showed that CVP+ and the composite ASITN/CVP assessment represented a strong predictor of a favorable clinical outcome (CVP+: OR 12.18 (95% CI 5.25 to 28.28); composite ASITN/CVP: OR 6.56 (95% CI 2.99 to 14.39)), together with IV thrombolysis and mTICI 2b–3. Therefore, the CVP could represent a marker of functionality of collaterals based on a physiopathological assumption.

Possible current and future applications

A growing interest in the analysis of the venous side of collaterals is seen in the literature. Faizy *et al* showed that a favorable profile of the cortical venous outflow assessed using the cortical vein opacification score (COVES) either CT angiography[23] or CT/MR perfusion[8] was associated with favorable collaterals and good functional outcomes after endovascular treatment of LVOs. Furthermore, Singh *et al*[24] concluded that the venous opacification over time assessed through the COVES in multiphase CT angiography was associated with good clinical results. The combined evaluation through this type of non-invasive imaging evaluation and the DSA assessment of the CVP could provide a more precise identification of fast and slow progressors.

Moreover, the evolution of stroke pathways toward a more rapid access to the angiosuite for MT, which is under evaluation in several trials,[25 26] could benefit from the introduction of an easy-to-use tool to assess collateral functionality as a prognostic factor. Besides, in patients with long delays (onset-to-groin and onset-to-imaging) due to secondary transfers, the use of CVP could provide further elements for the understanding of collateral circulation and patient selection in patients imaged several minutes or hours before.

Limitations

We acknowledge that the retrospective and single-center nature of the study represent the main limitations of the study. Furthermore, patients included in the study were selected according to specific criteria, which were necessary for the purpose of the study, such as the prolonged venous phase of the pretreatment angiograms and the absence of motion artifacts. Although the Quality Control core laboratory assured the strict selection of eligible patients, this could represent a potential inclusion bias.

CONCLUSION

CVP was associated with favorable baseline profiles and clinical outcomes after MT of anterior circulation LVOs. The composite assessment of collaterals through ASITN/SIR+CVP and CVP itself seems to provide a stronger correlation with favorable clinical outcomes compared with ASITN/SIR alone. In patients with good collaterals according to the ASITN/SIR scale, the presence of CVP was strongly associated with a favorable clinical outcome compared with the absence of CVP. These results confirm the findings that have been described in previous studies using non-invasive imaging and suggest that the evaluation of the venous phase could provide a solid contribution to the assessment of collaterals. If these results are confirmed in larger prospective studies, the assessment of CVP could enable improvement in the selection of patients.

Acknowledgements Dr François Zhu and Dr Marco Pileggi served as scientific advisors. Dr Luca Scarcia and Dr Isabella Kleibe provided and cared for study patients.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Comité Etique de Recherche de l'Hôpital Foch (Foch Hospital IRB) Reference number: IRB00012437. The IRB waived the need for informed consent to be obtained (retrospective analysis without information identifying participants).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request to the corresponding author.

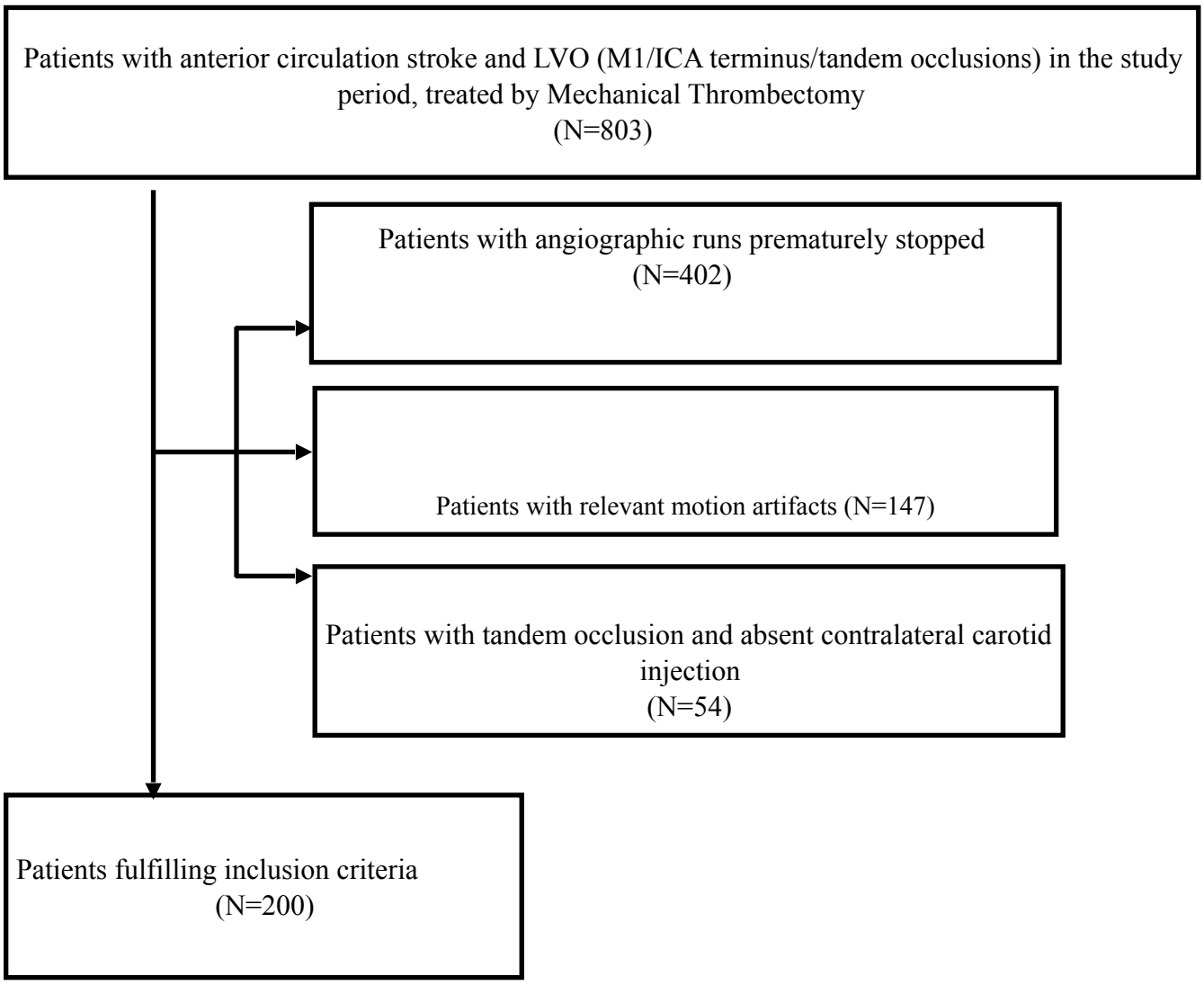
ORCID iDs
Arturo Consoli http://orcid.org/0000-0001-6640-8541
Alessandro Sgreccia http://orcid.org/0000-0002-0834-644X

REFERENCES

1 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
2 van Horn N, Kniep H, Leischner H, *et al*. Predictors of poor clinical outcome despite complete reperfusion in acute ischemic stroke patients. *J Neurointerv Surg* 2021;13:14–18.
3 Nogueira RG, Haussen DC, Liebeskind D, *et al*. Stroke imaging selection modality and endovascular therapy outcomes in the early and extended time windows. *Stroke* 2021;52:491–7.
4 Nguyen TN, Abdalkader M, Nagel S, *et al*. Noncontrast computed tomography vs computed tomography perfusion or magnetic resonance imaging selection in late presentation of stroke with large-vessel occlusion. *JAMA Neurol* 2022;79:22–31.
5 Ravindran AV, Killingsworth MC, Bhaskar S. Cerebral collaterals in acute ischaemia: implications for acute ischaemic stroke patients receiving reperfusion therapy. *Eur J Neurosci* 2021;53:1238–61.
6 Ospel JM, Volny O, Qiu W, *et al*. Impact of multiphase computed tomography angiography for endovascular treatment decision-making on outcomes in patients with acute ischemic stroke. *J Stroke* 2021;23:377–87.
7 Tong L-S, Guo Z-N, Ou Y-B, *et al*. Cerebral venous collaterals: a new fort for fighting ischemic stroke? *Prog Neurobiol* 2018;163-164:172–93.
8 Faizy TD, Kabiri R, Christensen S, *et al*. Favorable venous outflow profiles correlate with favorable tissue-level collaterals and clinical outcome. *Stroke* 2021;52:1761–7.
9 Higashida RT, Furlan AJ, Roberts H, *et al*. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke [Erratum in: Stroke. 2003;34(11):277]. *Stroke* 2003;34:e109–37.
10 Al-Ali F, Elias JJ, Filipkowski DE, *et al*. Acute ischemic stroke treatment, part 1: patient selection "the 50% barrier and the capillary index score". *Front Neurol* 2015;6:83.
11 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:e161–70.
12 Kim HJ, Lee SB, Choi JW, *et al*. Multiphase MR angiography collateral map: functional outcome after acute anterior circulation ischemic stroke. *Radiology* 2020;295:192–201.
13 Consoli A, Andersson T, Holmberg A, *et al*. CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study. *J Neurointerv Surg* 2016;8:1211–6.
14 Anadani M, Finitsis S, Clarençon F, *et al*. Collateral status reperfusion and outcomes after endovascular therapy: insight from the Endovascular Treatment in Ischemic Stroke (ETIS) registry. *J Neurointerv Surg* 2022;14:551–7.
15 Mangiafico S, Sala V, Nencini P, *et al*. Effect of the interaction between recanalization and collateral circulation on functional outcome in acute ischaemic stroke. *Interv Neuroradiol* 2014;20:704–14.
16 Liebeskind DS, Saber H, Xiang B, *et al*. Collateral circulation in thrombectomy for stroke after 6 to 24 hours in the DAWN trial. *Stroke* 2022;53:742–8.
17 Kaesmacher J, Maegerlein C, Zibold F, *et al*. Improving mTICI2b reperfusion to mTICI2c/3 reperfusions: a retrospective observational study assessing technical feasibility, safety and clinical efficacy. *Eur Radiol* 2018;28:274–82.
18 Kleine JF, Wunderlich S, Zimmer C, *et al*. Time to redefine success? TICI 3 versus TICI 2b recanalization in middle cerebral artery occlusion treated with thrombectomy. *J Neurointerv Surg* 2017;9:117–21.
19 Russo R, Del Sette B, Mizutani K, *et al*. Mechanical thrombectomy in distal residual occlusions of the middle cerebral artery after large vessel recanalization in acute stroke: 2b or not 2b? A pragmatic approach in real-life scenarios. *World Neurosurg* 2021;151:e793–802.
20 Ginsberg MD. The cerebral collateral circulation: relevance to pathophysiology and treatment of stroke. *Neuropharmacology* 2018;134:280–92.
21 van Horn N, Heit JJ, Kabiri R, *et al*. Cerebral venous outflow profiles are associated with the first pass effect in endovascular thrombectomy. *J Neurointerv Surg* 2022;14:1056–61.
22 Ravindran AV, Killingsworth MC, Bhaskar S. Cerebral collaterals in acute ischaemia: implications for acute ischaemic stroke patients receiving reperfusion therapy. *Eur J Neurosci* 2021;53:1238–61.
23 Faizy TD, Kabiri R, Christensen S, *et al*. Association of venous outflow profiles and successful vessel reperfusion after thrombectomy. *Neurology* 2021;96:e2903–11.
24 Singh N, Bala F, Kim BJ, *et al*. Time-resolved assessment of cortical venous drainage on multiphase CT angiography in patients with acute ischemic stroke. *Neuroradiology* 2022;64:897–903.
25 Pfaff JAR, Schönenberger S, Herweh C, *et al*. Direct transfer to angio-suite versus computed tomography-transit in patients receiving mechanical thrombectomy: a randomized trial. *Stroke* 2020;51:2630–8.
26 Requena M, Olivé-Gadea M, Muchada M, *et al*. Direct to angiography suite without stopping for computed tomography imaging for patients with acute stroke: a randomized clinical trial. *JAMA Neurol* 2021;78:1099–107.

Supplemental Material

Supplemental Fig.1. Flow chart of the study with eligibility criteria.



Supplemental Table 1. Subgroup analysis and multivariate analysis

	<60	**60-90**	**>90**
N patients	41	39	120
Age, mean ± SD	65.5 ± 17.2	69.8 ± 16.0	64.7 ± 15.4
Baseline ASPECTS, median (IQR)	7 (5-8)	7 (5-8)	7 (5-8)
CVP+, N(%)	23 (56.1%)	22 (56.4%)	45 (37.5%)
ASITN/SIR >2, N(%)	22 (53.7%)	23 (59.0%)	68 (56.7%)
mRS 0-2, N(%)	26 (63.4%)	19 (48.7%)	51 (42.5%)
N passes, mean ± SD	2.29 ± 1.54	2.41 ± 1.67	2.78 ± 2.26
Multivariate analysis: defined variable CVP+			
	OR	IC95%	*p*
ASITN/SIR >2	17.0	[6.3 - 46.3]	*<0.0001*
IV Thrombolysis	3.6	[1.5-9.0]	*0.0053*
Onset to imaging			*0.02*
180< vs <90	9.1	[2.0-41.7]	
90-180 vs <90	2.9	[0.98-8.53]	
Onset to groin			*0.0006*
180-360 vs <180	0.1	[0.04-0.47]	
360< vs <180	0.03	[0.005-0.195]	
	OR	IC95%	*p*
Age	0.97	[0.941-0.996]	*0.02*
CVP+	12.18	[5.25-28.28]	*0.001*
Composite ASITN/SIR + CVP	6.56	[2.99-14.39]	*0.001*
IV Thrombolysis	2.68	[1.17-6.14]	*0.02*
mTICI 2b-3	5.21	[2.86-9.47]	*0.006*

CVP+: Presence of collateral venous phase; mRS: modified Rankin Scale; PH1/PH2: parenchymal hematoma according to the ECASS-III scale

The findings of this study showed how the CC should be assessed not only according to its extension and that we should consider also their effectiveness.

As it has been shown in the previous chapter, also patients with good CC (according to the ASINT/SIR classification) may not reach functional independency although these may represent the optimal candidates to achieve favorable clinical outcomes.

In order to assess the effectiveness of the CC we have proposed the analysis of the CC based on the concept of the potency of the venous side of collateral vessels. According to this theory, the effectiveness of the CC would also relate to the effectiveness of the venules of the collateral circulation performing several tasks, such as the clearance of the downstream emboli, the maintenance of the blood flow and a preventive effect on platelet adhesion (*Tong et al., 2018*).

Furthermore, the patency of the venous side of the collateral circulation is related with the possibility for the CC to continue to "accept" the blood flow retrogradely from the pial circulation, avoiding a condition of stasis in the microcirculation with a subsequent risk of thrombosis.

The current study showed that the analysis of the venous phase of collaterals seems to refine the evaluation of CC. Although the ASITN/SIR-based analysis and the CVP-based analysis showed globally similar results, in line with the literature (*Anadani et al. 2022, Mangiafico et al. 2014, Liebeskind et al., 2022*), it was possible to observe a stronger association between the presence of CVP (CVP+) and the measures of clinical outcomes (3 months mRS) or hemorrhagic transformation rather than the evaluation performed through the ASITN/SIR score.

Furthermore, the composite analysis that matched the combined evaluation of the CC through both the ASITN/SIR and the CVP provided solid results in terms of association with favorable clinical outcomes (OR: 6.56, IC95%[2.99-14.39]) and a lower risk of hemorrhagic transformation.

Interestingly, in the inclusion period of the study (2016-2021), we had to exclude about 400 patients from the analysis because of the lack of angiograms sufficiently durable to assess the venous phase of the collateral circulation. Although that could represent a potential limitation for the present study, this datum depicts the poor interest that has always been paid in the past decades to the venous side of the CC.

An external validation of these results will be mandatory in order to confirm these findings, which remain at the moment a hypothesis-generating tool.

The CC should be considered as a dynamic circulation, retrogradely running from the neighbor vascular territories towards the territory of the occluded artery.

Digital Subtraction Angiography provides the visualization of the cerebral circulation through the opacification of the vessels thanks to the contrast agent and it could be considered particularly suitable to assess the CC.
Indeed, DSA provides a real-time imaging of the transit of the contrast agent, highlighting the different phases of the blood flow: the arterial phase, the parenchymal phase and the venous phase. Therefore, DSA is capable to provide a dynamic assessment of the CC as well.

During the PhD program, after having reviewed several angiograms and with the clinical experience as interventional neuroradiologist of the academic work on collaterals, I have been working on the introduction of two novel concepts in the assessment of the CC: the desynchronization and the turning points.

The ***desynchronization*** of CC depicts the different behavior of the CC as compared to the "normal" cerebral circulation, namely the anterograde circulation. Indeed, the CC is a retrograde circulation per definition and, therefore, the time of opacification is delayed than the one needed for the normal cerebral circulation **(Fig. 9**).
Consequently, the CC and the cerebral circulation are visualized in different phases of the angiograms and these could be considered as "desynchronized".

It could be intuitive that the shorter is the delay between the opacification of the normal anterograde circulation and the appearance of the CC the higher the flow velocity will be in the CC and then in the ischemic territory.

Theoretically, this feature could be interpreted as a marker of effectiveness of the CC. Indeed, according to the aforementioned theory by Tong et al. (*Tong et al., 2018*), the patency of the venous side of the CC allows to avoid a blood stasis in the CC and to maintain an effective blood flow in the ischemic territory and the perfusion of the microcirculation.

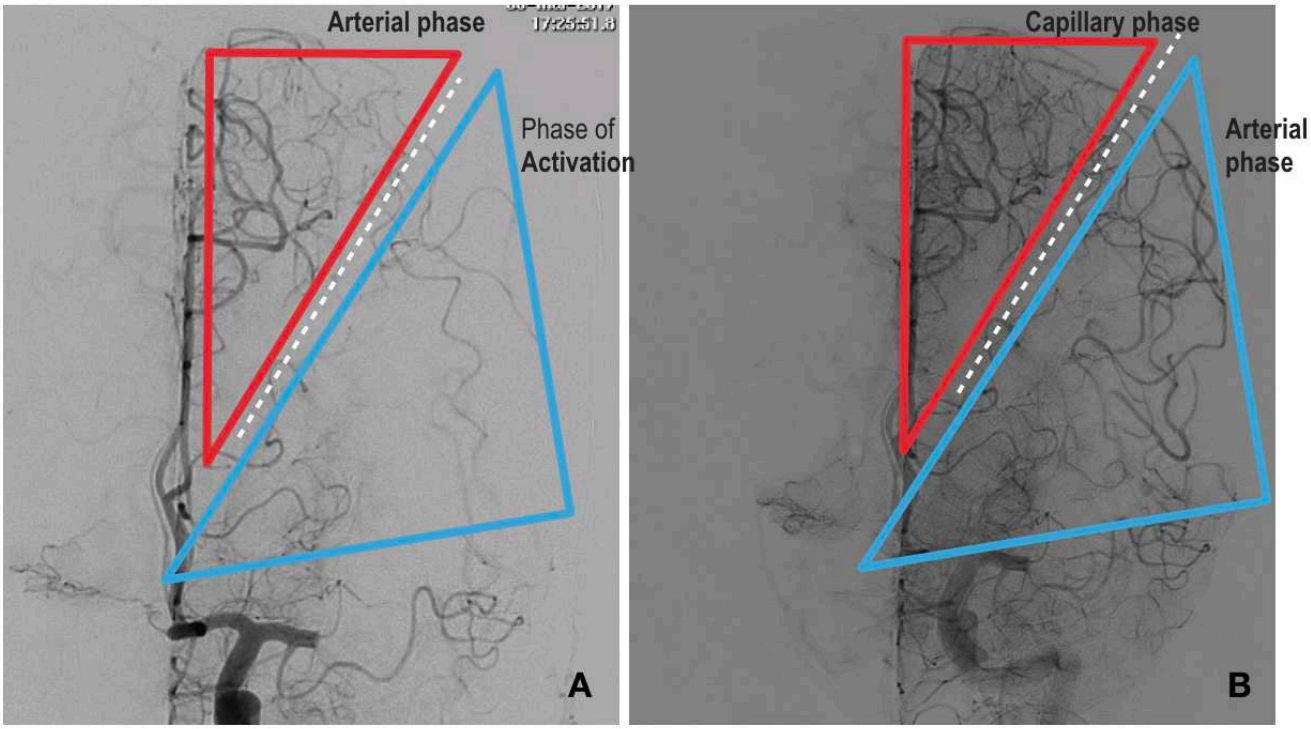


Fig. 9. *The desynchronization of the collateral circulation* (from "*Lo studio dei circle collateral può sostituire le tecniche di imaging per identificare la penombra nella selezione dei pazienti da sotto-porre a TM nelle finestre terapeutiche più lunghe?" - Arturo Consoli - Invited Conference at the 8th National Congress of the Italian Stroke Association, Verona - December 2021)* .
Digital Subtraction Angiography, antero-posterior projection, acquired in a patient with a left M1-Middle Cerebral Artery occlusion. Panel A shows the very early arterial phase of the angiogram: at this moment of the acquisition we can observe how the "normal" anterograde cerebral circulation (highlighted by the red triangle and corresponding to the territory of the Anterior Cerebral Artery) and the collateral circulation (blue triangle highlighting the collateral area) are desynchronized. Indeed in this early phase the collateral circulation is in the activation phase while the normal cerebral circulation is the arterial phase. Panel B shows the intermediate (capillary) phase in the normal cerebral circulation; in this phase the collateral circulation is in the arterial phase.

The progression of the contrast agent through the cerebral circulation can be clearly divided into three different phases: arterial, parenchymal/capillary blush and venous. The transition between either two consecutive phases is therefore defined as **a turning point** of the two phases. In 2D pre-treatment DSA, such turning points represent the frames of the angiograms where the transition from an angiographic phase to the following can be observed according to the opacification of the vascular structures (arteries, capillary blush, veins).
The turning points would help to differentiate the transition from the arterial to the parenchymal phase and from the parenchymal to the venous phase. Thus, the application of the turning points

would help to separate and to differentiate the angiographic phases and it could provide the basis to "quantify" the desynchronization between the CC and the cerebral circulation.
The introduction of these two concepts seems to be a suitable approach to assess a dynamic process, such as the CC function.

Future perspectives

The detection of the CVP seems to increase the diagnostic performances of the currently most used classification for CC.
The introduction of the desynchronization and the turning point could represent an advancement in the understanding of the hemodynamics of the CC. Indeed, these concepts could help to "decompose" the assessment of the CC and could provide some measurable parameters in order to quantify the effectiveness of the collateral vessels and, hopefully, to calculate the flow velocity within the CC.

Furthermore, the main advantage of the angiographic analysis lays in the real-time imaging provided by the DSA. The assessment of the CC performed through the DSA would not be influenced by other delays, since it would be performed at the beginning of the procedure of Mechanical Thrombectomy.
Indeed, data that are currently reported in terms of correlation between the baseline extension of the ischemic area (i.e. DWI-ASPECTS or plain CT-ASPECTS or CT-Perfusion ASPECTS) and the angiographic evaluation of collaterals in the Angiosuite are definitely biased by the latency between the baseline neuroimaging and the beginning of the angiographic assessment (transfert time, setting, eventual general anesthesia etc…). As we have observed in the paper, it seems that the patency of the CVP decreases over time, which could be interpreted as a dynamic modification of the CC evolving towards a mechanism of in-situ thrombosis (*Consoli A et al., The angiographic collateral venous phase: are good collaterals always effective? Supplemental Table 1, submitted to JNIS*).

Moreover, the new trend that is currently under investigation in some randomized trials (*Pfaff et al. 2020; Requena et al. 2021*) is to consider a direct access of stroke patients directly to the Angiosuite, waiving the preliminary selection process through the CT/MRI. According to this schema, DSA would assume a more central role in the identification of markers of effectiveness and prognosis rather than the current role.

The detection of the turning points, in particular, could be a substrate for automated algorithms that would be capable to reproduce the assessment of the transition of the angiographic phases and then to detect the presence of the CVP in the area of the CC.

Finally, the evaluation of a correlation with CT-Perfusion and MR-PWI are mandatory in order to strenghten the results of the critical analysis of the angiographic assessment of the CC, as well as a comparative assessment with the new imaging techniques such the evaluation of the profile of the cortical venous outflow assessed using the cortical vein opacification score (COVES).

All these findings could support the theory that the venous phase of the collateral circulation could represent the real modulator of the evolution of the ischemic process and that the representation of a good or of a poor collateral circulation could depend mainly on the effectiveness and permeability of the venous outlet of the CC rather than the extension of the arterial leptomeningeal anastomoses.

5. A TECHNICAL APPROACH TO COLLATERALS BASED ON PHYSIOPATHOLOGY: DEVELOPMENT OF AN ALGORITHM FOR THE ANGIOGRAPHIC EVALUATION OF THE COLLATERAL CIRCULATION

The results of the clinical and critical analysis of collateral circulation, which were discussed in the previous chapters, raised several questions about the assessment of collateral circulation.

Indeed, the current methods to assess the CC may not provide a definite answer to the main physiopathological issues, such as the effectiveness of collaterals, the role of the venous phase of the CC and its capacity to properly sustain the cerebral perfusion although their extension.

Furthermore, the growing interest in a more rapid workflow for the management of acute ischemic stroke will put in a central position the role of the DSA in patients' assessment in the acute setting of AIS. This effort considers the direct access to the Angiosuite avoiding the intermediate diagnostic step based on the CT or MRI. However, this type of pathway needs to be further investigated and its applicability worldwide will be a matter of discussion considering the different geographical setting and the available human resources.

It would therefore be really advantageous if the pre-treatment DSA acquired in-situ can be used to provide indications of treatment strategies, such as selecting patients for MT, prognosis, strategies after the treatment, etc. This will in the end involves the development of a DSA-based dedicated algorithm to characterize the CC. This algorithm will be constructed according to the physiopathological assumptions that have already been discussed. To achieve this, the pre-treatment dynamic DSA series need to be quantitative analyzed. In particular, this analysis will try to look for the potential link between image features and the concept of *deysnchronization* between the cerebral and collateral circulation and the concept of the *turning points*.

Inspired by and as an extension of the M2 work, in this chapter we will first observe the time-density curve of the collateral region of the DSA data. Different from only a ROI based study, pixel-wise analysis will be also applied. Parametric maps and image based features will be computed and analysed, and coorelated with the radiological readings of these data. A tissue-specific (i.e. parenchyma artery, or veins) will then be made following the segmetion of vessels within in the collateral region as previously proposed in **Fig. 6** (Section II – Chapter 2, p.33).

5.1. Materials: Study population and image acquisition protocol

5.1.1. The study population and image analysis

One-hundred and eight patients with the occlusion of the M1-middle cerebral artery segment (M1-MCA) eligible to MT procedure with a M1-MCA occlusion between 2018 and 2021 from Hospital FOCH centre in the ETIS Registry (NCT03776877) were included in this analysis. Patient exclusion criteria was restricted to be minimum in order to analyse a mixed population of patients with good or poor collaterals, or age, therefore the timing, in particular the delay between the onset of symptoms and the beginning of the procedure of MT (onset-to-groin).
All patients were imaged through a 6 frames/second acquisition (as defined in Chapter 2) as the first angiographic run before starting the MT procedure.

Afterwards, a dedicated Quality Core Lab, which included two neuroradiologists not involved in the procedures, evaluated the quality of the images and stated whether to include the angiogram in the analysis. Motion artefacts represented the main reason for exclusion and 19 patients were excluded from the analysis.

Baseline and follow-up clinical data were prospectively collected from the ETIS Registry (NCT03776877). The local Institutional Review Board approved the study and waived for written informed consent. All the data were stocked in a dedicated database and the images were anonymized and centralized inside the ArchiMed system hosted by the IADI laboratory, Nancy, France.

5.1.2. The DSA acquisition protocol

The adopted imaging protocol was the same as already used in the pilot study described in Chapter II (page 31). The Antero-Posterior view of the pre-treatment angiograms acquired with 6 frames/s were collected from the recruited population. As previously described, only the AP view was used for the analysis in order to avoid the overlap with the ACA territory in the lateral projections.

Indeed, it could be intuitive to observe that the flow density curves obtained by the segmentation of the vessels opacified using an “experimental” DSA acquisition protocol at 6 frames/second were more detailed that those obtained using a “standard” acquisition protocol at 2 frames/second. Both

acquisition protocols are available on most of the angiographic machines although the standard acquisition protocol is set at 2 frames/second.

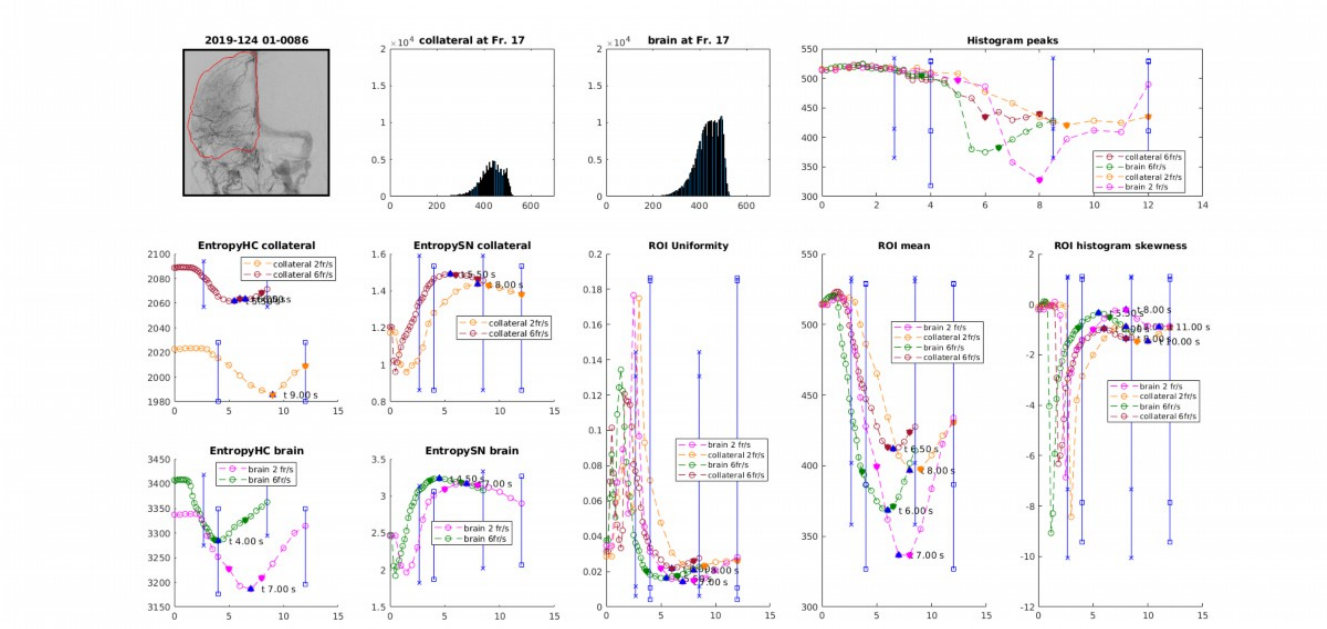


Fig. 10. *Comparative analysis between the standard acquisition protocol (2 frames/second) and the experimental protocol (6 frames/second). The analysis of the curves showed that the experimental acquisition protocol provided more informative curves since a larger number of data is available for the analysis of pixel density modification in the same interval time.*

This observation seems to be particularly relevant if we consider the dynamic behavior of the CC, since a higher number of frames provides more data in the same time interval, allowing the construction of a more precise curve.

A panel of variables have been studied to perform the critical analysis of the angiograms for the setting of the algorithm. These variables were summarized in the analytic plan that was set and named as "Image Feature Analysis (IFA)", which will be described later.

The analysis of a subgroup of patients imaged with both conventional clinical acquisition protocols (2 vs 6 frames/second) showed the difference in the construction of the perfusional curves (**Fig. 10**), highlighting how the perfusional curves obtained through the experimental protocol were more informative and provided more data. In particular, the 6 frames/second protocol provided a higher number of images to be analysed in the late venous phases, which would determine a more reliable result overall in terms of detection of the collateral venous phase.

For these reasons, a 6 frames/second acquisition protocol was used.

In order to characterise the angiograms, especially the contrast enhancing time-course, we have thoroughly analysed the behaviour of the DSA series, not only by regions (cerebral, collateral region, watershed region, etc.) but also by pixel in order to understand the contrast behaviour by tissue. Thus for each patient, their data have been divided into different regions and the contrast progression has been classified as described in the three-phase scheme already described in the previous chapters.

5.2.1. Spatial analysis the observed regions

We analyzed the imaging features in 4 types of regions: cerebral region, extended collateral region, the watershed regions and pure collateral regions (see details definition as below, **Fig. 11**), in order to observe the time course changes of contrast agent filling of collateral vessels in the cortical MCA region:

- Cerebral region: a ROI was drawn including the whole hemisphere perimeter including the temporo-basal pole, the inferior border passed through the ICA siphon.

- Extended-collateral ROI (large, red one) including the vascular territories of the ACA and the MCA, drawn from the midline and following the outer profile of the cortical convexity and the inner profile of the white matter territory, excluding the basal ganglia territory medially and the fronto-basal area inferiorly. A careful selection was performed excluding the superior sagittal sinus superiorly and the transverse sinus inferiorly in order to avoid a selection bias of these venous structures that could have influenced the modification of the pixel density. This ROI would provide data about the density curves related to both the cerebral and the collateral circulation.

- Pure collateral ROI (blue one, intermediate ROI), which included only the territory of the MCA. This type of ROI could limit the influence of the cerebral circulation (which was identified with the ACA territory, **Fig. 9**, Chapter 4, p.85) and provide data related to the density curve of the collateral area alone. The pure collateral ROI is overlapped with the extended collateral ROI.

- Watershed ROI (yellow one, more restricted), which was drawn at the level of the transition from the ACA to the MCA territory (watershed territory). This ROI could provide information about

the density curve of the watershed territory, which can be considered as the area of activation of the collateral circulation in case of M1-MCA occlusions.

All the segmentation process in the initial phase was performed manually using the freeware ITK-SNAP.

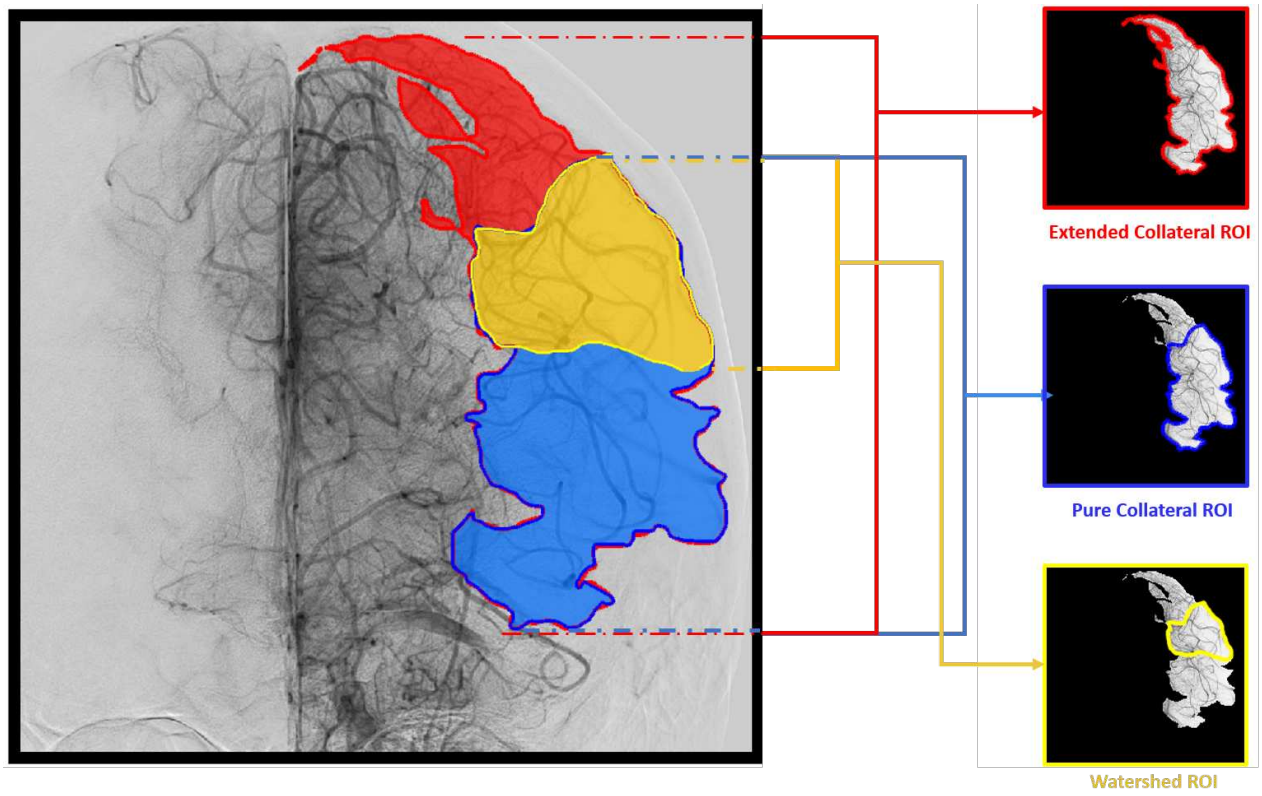


Fig. 11. *Digital Subtraction Angiography, anteroposterior view showing the occlusion of the left middle cerebral artery. Depiction of the three ROIs that were compared for the analysis of the collateral circulation: the large ROI (red), the intermediate ROI (blue) and the critical ROI (yellow). The three ROIs are overlapped.*

5.2.2 Temporal analysis: the observed time window and key frames

According to the concept of the desynchronization, the collateral and the cerebral circulation have a different time window of observation. In the study both time windows were labelled and were identified through the first and the last frame of appearance of the opacified vessels. The first turning point corresponds to the transition between the arterial and the parenchymal phase and the second one to the transition between the parenchymal and venous phase. Some landmarks were used in order to define the turning points and are summarized as follows (**Fig. 12**):

- Cerebral circulation

First turning point: first frame of observation of the parenchymal blush in the ACA territory

Second turning point: first frame of visualisation of the superior longitudinal sinus on the midline

- Collateral circulation

First turning point: first frame of observation of the parenchymal blush in the CC ROI

Second turning point: first frame of visualisation of the cortical veins, which have a straight course parallel to the visualisation of the cerebral sulci.

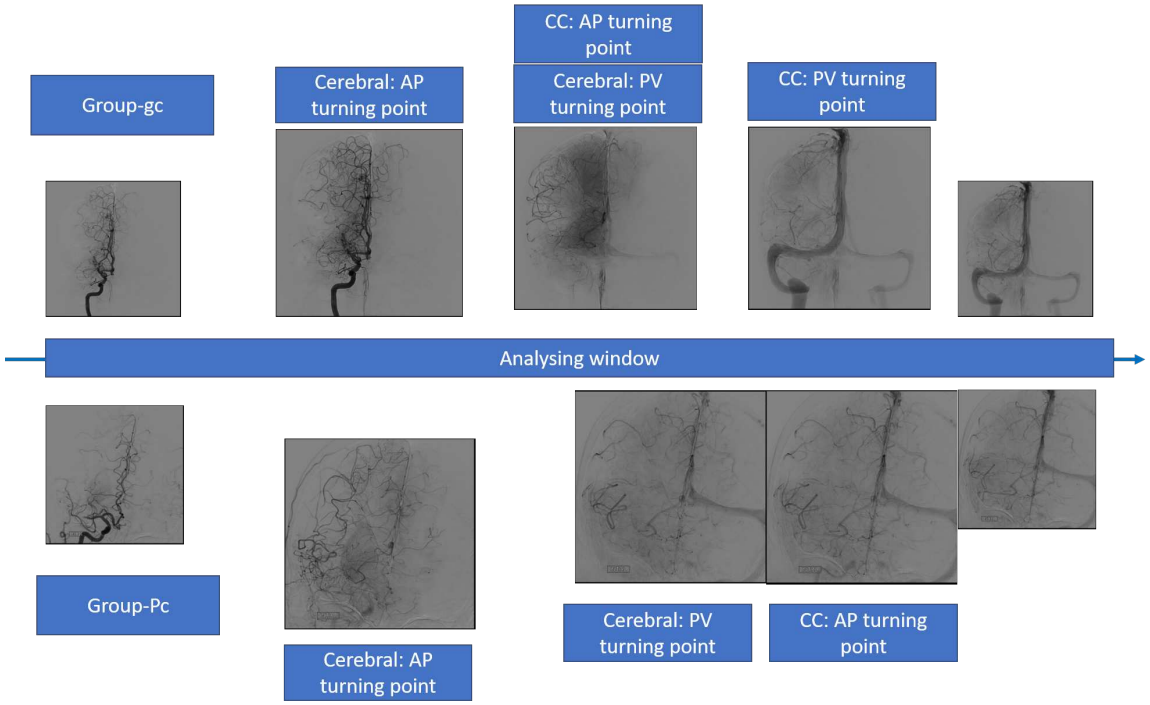


Fig. 12. *Definition of the turning points in the cerebral and collateral regions according to the concept of the desynchronization*

5.2.3 Summary and contribution

I have set up the protocol of analysis of angiograms by defining the observation of the turning points and successively analysed the angiographic runs for the whole population in order to manually define:

- the ROIs (collateral and hemispheric), according to the Master2 protocol
- the first and the last frame of observation of the collateral circulation, in order to define the temporal window of observation

- the turning points, in order to compare the manual detection of the transition of the circulatory phases on the angiograms with the assessment performed by the algorithm. Two turning points were defined for both cerebral circulation and CC.

5.3. Semi-quantitative time-density curve analysis

Assessment of the ROI-based time-density curve analysis is done by computing the following parametric maps: Time-to-peak enhancement map (TTP), mean transit time map (MTT), and maximum enhancement projection map (MEP) as shown in **Fig. 13**. While interpretations were difficult to make on TTP and MTT data, MEP images resulted more indicative to give the first intuitive explanation of "good" and "poor" collaterals (named as *Group-gc* and *Group-pc*).

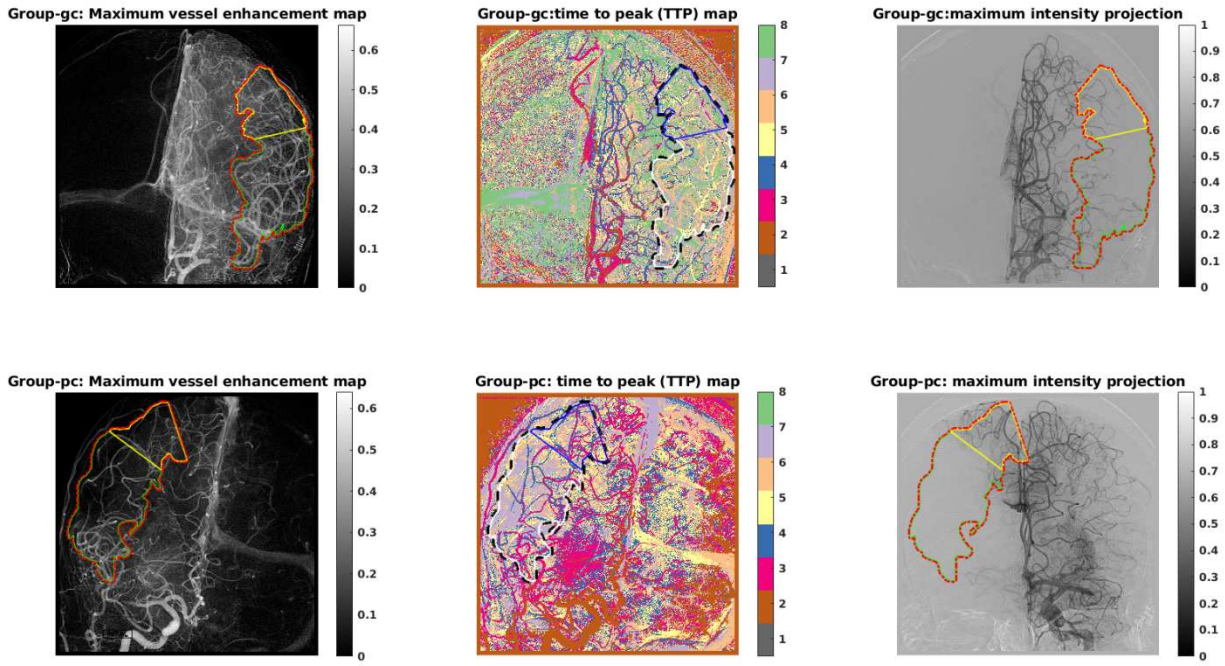


Fig. 13. *ROI-based analysis of time density curves in patients with good collaterals (superior row) and poor collaterals (inferior row) according to MEP maps (first image of both rows) and TTP maps (second images of both rows).*

Examples from the two groups (Patient TEST-002 and Patient TEST-041 representing good and poor collateral groups respectively) are illustrated in **Fig. 13**. It is most interesting to notice that in the MEP map, the collateral region of *Group-gc* contains more dense vessels and that we can observe an opposite situation in *Group-pc*. In the current calculation, the MEP is extracted basing on all the frames, and the current CC status (good or poor) is assessed by the arterial collateral status.

However, whether we consider also the venous phase or not, that would not lead to obvious differences in the MEP map.

5.4. Vessel complexity in the collateral region

In other to quantitatively depict the previous observation and also prove our hypothesis that the good/poor CC can be discriminated by the CC vessel complexity level, we used the metric called "fractal dimension",D_s, a recent mathematical method which has been widely used to quantify retinal vessels and trabecular bone patterns in X-ray or CT (*Mainster MA, 1990*; *Jurczyszyn K et al., 2012; Majumdar et al., 1999*). An intuitive and practical understand of fractal dimension is that it describes how thoroughly it fills space. The calculation of fractal dimension here uses the FracLab (version 2.2, MATLAB toolbox; *https://project.inria.fr/fraclab*), a classical box counting method but can directly applied to grey-scale images. The equation used to calculate D_s is reported here below:

$$D_s = \lim_{\varepsilon \to 0} \frac{\log N(\varepsilon)}{\log\left(1 / \varepsilon\right)}$$

where D_s is the fractal dimension, ε is the length of box which creates mesh covering surface with examing pattern, $N(\varepsilon)$ is the minimal number of boxes which are required to cover examining pattern.

As previously observed in the previous section, the distal part of the pure collateral ROI provided the most relevant results in terms of differentiation between good and poor CC. A sub-analyis of this ROI was then performed. Therefore, we calculated the fractal dimension $D_s$of three sub-regions of the pure collateral ROI (**Fig. 14**): 1. Pure collateral ROI (in red), 2. Watershed ROI (in yellow), 3. ROI 1 without ROI2 (in green). This was also because some of the patients, mainly those with poor collaterals, showed very dense watershed regions, although in the adjacent distal CC region only few vessels were observed.

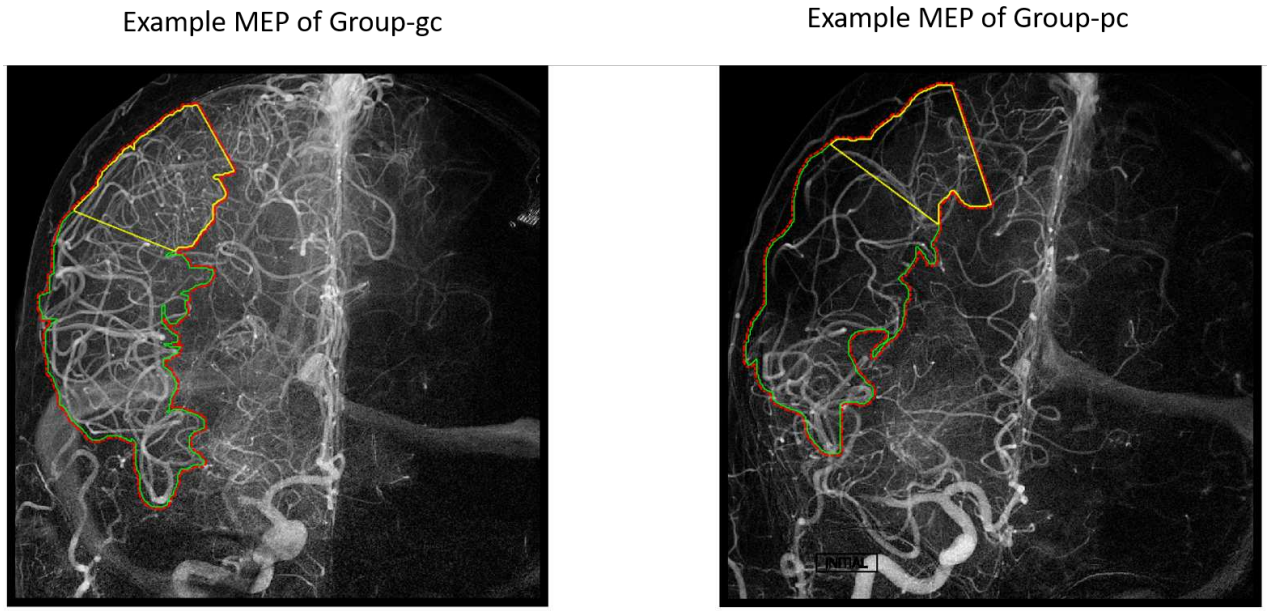


Fig. 14. *Illustration of the three ROIs for fractal dimension calculation. The left image depicts the ROIs in a patient belonging to the Gc (good collateral group) and the right one is referred to a patient belonging to the Pc (poor collateral group).*

Thus it is necessary to make a thorough observation. The D_s of this three ROIs in the two groups (Group-Gc and Group Pc) are plotted in **Fig. 15A**. Since the relative size of the collateral region within the cerebral may vary from patient to patient and that could introduce a bias, we also calculated the normalized fractal dimension by dividing the ratio of CC and cerebral areas (**Fig. 15B**).

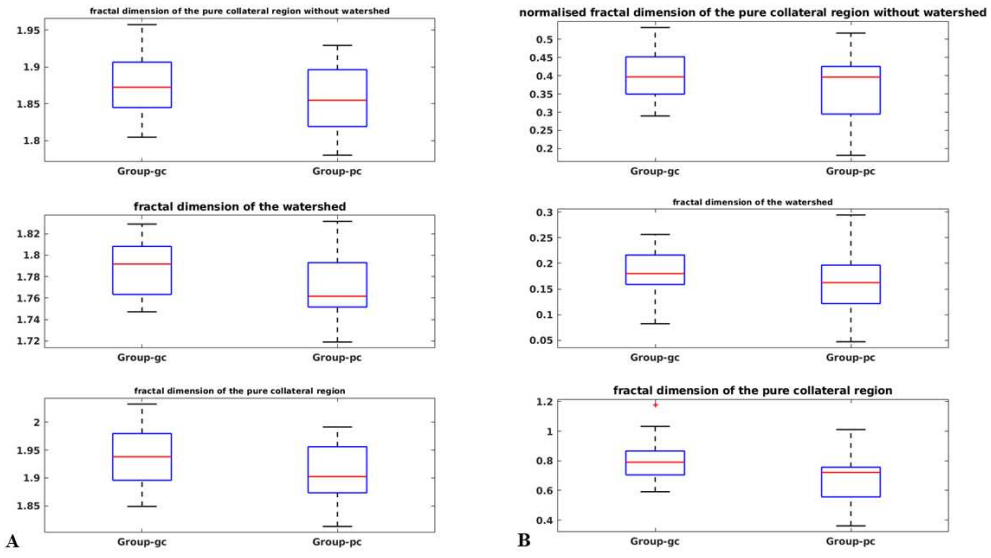


Fig. 15. *Boxplot of the fractal dimension in the three ROIs between the two groups (A) and the normalized fractal dimension between the two groups (B).*

According to the boxplot above, the normalized fractal dimension of the pure CC ROI ($nD_s(pCC)$) seems to be a good candidate to separate Group-gc and Group-pc. An Anova test was then applied to the ($nD_s(pCC)$ of the groups, leading to a p = 0.013 (p = 0.05 is considered as significant),showing the two groups are significantly different (**Fig. 16**).

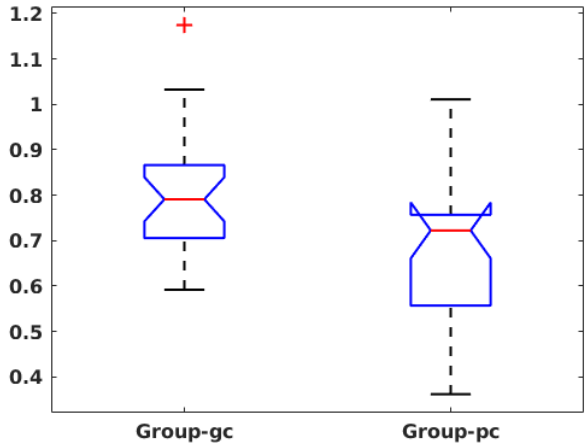


Fig. 16. *Anova plot showing the normalized fractal dimensions in both subgroups.*

5.5 The Image Feature Analysis (IFA)

As aforementioned, a list of imaging features has been carefully chosen in order to characterise the CC regional intensity behaviour during the contrast progression through the different circulatiory phases of the DSA. Another objective of the IFA was to provide an intepretation of the physiopathological concepts that were introduced: the desynchronization and the turning points.

In either the CC ROI or the cerebral ROI, the evolution of the contrast trajectory is in general described as follows: the image intensity starts to decrease when the contrast starts to fill the arteries, and the anatomical information including the vessel networks starts to be enhanced.
The amount of information increases the number of vessels being enhanced, their sharpness increases until the maixum value is ahiceved and that will represent the end of arterial phase and the beginning of parenchyma phase, which corresponds to the first turning point. From that point, the contrast agent starts to leave the artery and to fill the capillary bed, where the perfusion to the parenchyma happens. This parenchymal phase causes the whole DSA image to become darker and darker, and the contrast between vessels and other tissues becomes less obvious.

However, due to the overlapping nature of DSA being a 2D-image, and to the delay between different regions (the cerebral and the CC region desynchronization as previously described), it may be the case that the parenchyma would be perfused progressively especially when the CC flow is slow.

After the DSA frame becomes the darkest and the less contrasted, the contrast agent starts to leave the parenchyma and entering the venous circulation. This represents the turning point from the parenchyma phase to the venous phase. At this time, the desynchronization between cerebral and CC regions would be the more obvious, with the worst case that before the end of the DSA acquisition which is defined as the full visualization of the dural venous sinuses (superior sagittal sinus and transverse sinuses), the venous phase of CC is still not shown.

The following image features are analysed: maximum histogram peaks change over time, the ROI intensity uniformity, mean and histogram skewness, and the entropy. As it was shown in **Fig. 10**, the IFA was based on several parameters:

The maximum *histogram peaks* at each frame in the CC and cerebral ROIs changes as the well as opacification when the contrast trajectory evolves. This curve starts to decrease when the contrast fills the arteries in the corresponding ROIs and starts to come back when the contrast leaves the ROI identifying a bi-phasic peak corresponding to the phase separation from the arterial to the parenchymal/capillary phase and from the parenchymal/capillary phase to the venous phase.

A particular mention will be done concerning the *entropy*. It is a scientific concept as well as a measurable physical property that is most commonly associated with a state of disorder, randomness, or uncertainty. The general definition of entropy can be found in the entropy focus criterion (*Atkinson et al., 1999*), which is used in order to favor the high contrast between the structures:

$$E = -\sum_{j=1}^{s} \frac{B_j}{B_{\max}} \ln\left[\frac{B_j}{B_{max}}\right]$$

However, entropy is also commonly described as a criterion of maximization in order to provide a noise reduction, according to a different formula, which therefore, this definition is a smoothness measurement:

$$E = \sum_{j=1} p_j * log_2\left(p_j\right)$$

In the construction of the algorithm we defined the entropy focus criterion as Entropy-HC (as "high contrast") and the criterion of maximization as Entropy-SN (as "smoothness").

The assumption used here is that when the contrast agent enters the collateral circulation region, the information content in the collateral area will be perturbed due to the modification of the opacification and thus lead to a change of entropy.

When there is a transition through the different circulatory phases, such as from artery to parenchyma, and from parenchyma to the venous phase, a dramatic change on entropy can be found.

The analysis of these ROIs showed that the results were not significantly different (**Fig. 17**). Indeed, according to the IFA panel, the shape, the slope and the valleys of the perfusional curves obtained through the three different ROIs did not differ.

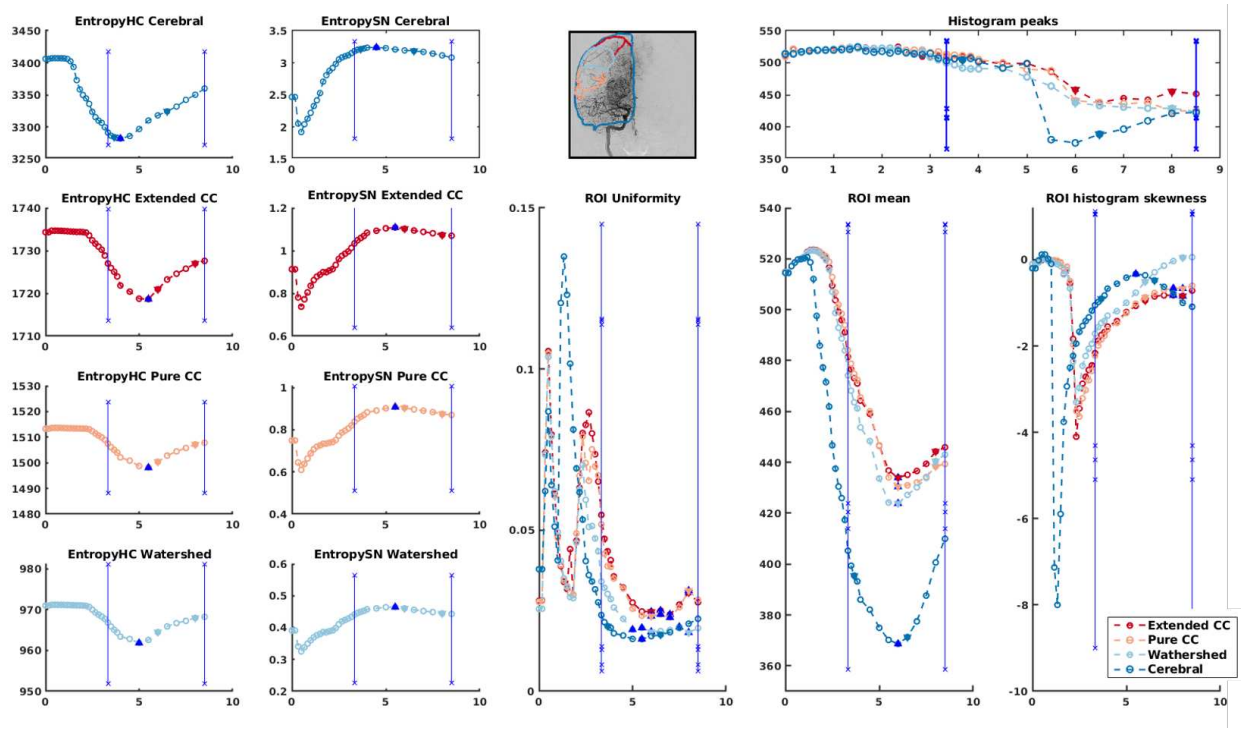


Fig. 17. *The comparative analysis of the three different ROIs using the IFA panel. A fourth ROI is referred to the hemisphere (named as "brain" ROI), which is used for normalization of the curves. No difference was observed in the behaviour of the perfusional curves.*

Although no difference was observed in terms of behaviour of the perfusional curves, the "Extended collateral" ROI was chosen for the setting of the algorithm for three main reasons:

- this ROI provides data from both types of circulations (cerebral and collateral), following the principle of the desynchronization;

- this ROI provides data for the detection of the venous phase, while the other two ROIs could miss this type of information being more limited;
- The extension of the ROI seemed to be the most reliable in order to perform the normalization with the hemispheric ROI in order to assess the real extension of the collateral area.
- In this context, we used entropy as a measurement of information content in a corresponding area.
- The hypothesis here is that the perfusion of phase contrast changes the information content of the collateral circulation area. The dramatic change of entropy value in this area should correspond to a local extreme (either a peak or a valley) in the function of entropy against time or the differential of this function. In the case of the DSA, after the contrast agent enters the ROI of the collateral circulation, the information content in the ROI changes, therefore the starting frame of the collateral circulation window corresponds to the inflection point of the entropy curve in **Fig. 17** (Entropy HC graph). The peaks of the entropy curve may therefore indicates the turning points.

Therefore, by drawing the entropy change according to each frame, it may be possible to detect the following features:

1. the *beginning of the collateral circulation window* by observing the change of the shape of the entropy curve along the time

2. the *turning points* from the arterial phase to the parenchymal/capillary phase or from the parenchymal/capillary phase to the venous phase, according to the following considerations:

a. The changing trend of the entropy curve will be altered, i.e. a local extreme (turning point) can be detected. More precisely, after entering the collateral area, the contrast agent starts to render the arteries. Thus, the appearance of this region starts to become more opacified from the initial flat grey with clear information of the arteries (activation phase). Therefore, following the first perturbation of the information content of this region, the entropy change within the collateral circulation area as well as the tendency of entropy change should be almost monotonic between the beginning of the collateral circulation perfusion window and the turning point from the arterial to the parenchymal phase. Indeed, the contrast bolus passing through the artery has highlighted the contrast between the structures. Thus, when all (or the largest part of) the arteries have been filled, the entropy within this region should be the smallest.

b. When the bolus starts to spread into the parenchyma, the image starts to be blurred. Indeed, the contrast agent starts to leak into the parenchyma and smooths out the corresponding region in the angiogram. Therefore, the entropy curve will show opposite trend compared the one observed in

the arterial phase. Such trend will stop when the parenchyma is fully perfused and the contrast starts to go to the viens. So, in that case, the turning point should correspond to the time when the entropy curve shows a local extreme, with a maximum value of the Entropy-HC.

For the Entropy-SN, the trend of the curve should be similar however it will be more evident concerning the transition from the parenchymal/capillary phase to the venous phase as it corresponds to the smoothest time of the whole perfusion state.

As far as the Point 1 is concerned, we found an excellent correlation between the beginning of the collateral phase identified by the algorithm and the one that was manually detected in almost all the current patients.

In this patient (TEST-002, **Fig. 18**), the two blue vertical lines correspond to the manual defined collateral circulation window, whereas the point on the red spot curve indicates the turning point of this curve (plot of Entropy), suggesting the transition of the phase from the arterial to the parenchymal phase and corresponding to the valley of this curve. This can probably be detected by looking at the peaks on the derivative of this entropy curve.

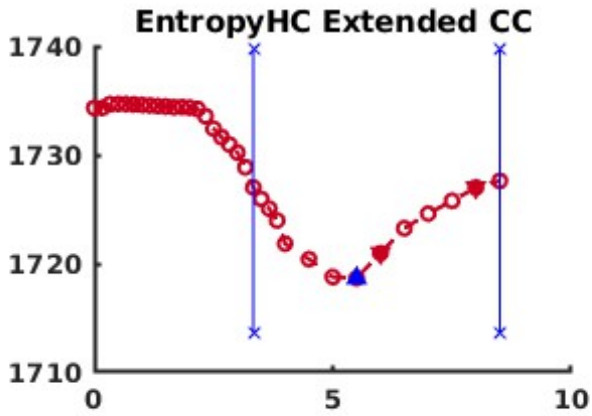


Fig. 18. *The Entropy plot in the collateral area. The blue lines identify the temporal window observation, manually defined. The blue triangle shows the turning point from the arterial to the parenchymal/capillary phase.*

Although we could achieve an excellent agreement in the detection of the frame corresponding to the beginning of the temporal window of observation (phase of activation), the end of the temporal window of observation was not easy to identify.

After the review of the patients for which it was not possible to identify the last frame of observation of the collateral circulation, we could conclude that this occurred almost in all patients with a

poor collateral circulation, with a limited arterial phase and almost absent parenchymal and venous phase.

These results represented the base for the development of the different versions of the algorithm and also the first step of integration of the novel concepts that were introduced.
The goal of the algorithm will be to provide a real-time analysis of the CC through the identication of the markers of effectiveness, such as the presence of a collateral venous phase, and to assess the flow velocity in order to describe the hemodynamics of the collateral vessels.

The development of the algorithm was the object of a patent submission procedure, which is on-going.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

The role of the collateral circulation in AIS has been widely investigated in the past and recent literature.
Although several articles and studies found strong correlations between the collateral status and the clinical outcome of patients treated by mechanical thrombectomy, the physiopathological mechanism of collaterals remains poorly understood.

Recently, the hemodynamic features of these leptomeningeal anastomoses made the subject of further investigations, leading to a more dynamic vision of the collateral vessels in the physiopathology of acute ischemic stroke.

However, the current tools to assess collaterals seem to be still limited and focused on the extension of the collateral vessels and the introduction of novel concepts and parameters to analyze could provide more reliable and solid results.
Indeed, as we have observed in the previous chapters, patients harboring a good collateral circulation may not benefit from the endovascular treatment through mechanical thrombectomy, although these patients would represent the best candidates to achieve a good clinical outcome.
A partial response to this issue could be to find in the limited assessment of collaterals according to the currently used grading systems, such as the ASITN/SIR classification.
Furthermore, these results strenghten the concept that extended collaterals may not be sufficiently effective and that a physiopathology-centred assessment is crucial to better understand the role of collaterals in acute ischemic stroke.
Thus, the integration of specific data concerning the effectiveness of the collateral circulation could improve the overall assessment of these anastomoses.

The introduction of the concepts of the *desynchronization* between the collateral circulation and cerebral circulation, the *turning points of the contrast trajectory phases*, as well as the evaluation of the *collateral venous phase* could provide a more complete analysis of collaterals and, potentially, a substrate for a real-time assessment of collaterals in the angiosuite.
The development of an automated algorithm to characterise the hemodynamic behaviours and to characterize the effectiveness represented the final goal of the Thesis.

The efforts that have been done in the setting of this algorithm have been driven by the physiopathological assumptions concerning the collateral vessel in order to provide useful information about their hemodynamic features in order to facilitate their understanding.

The patent application, whether accepted, will enable the setting of multicentric evaluations based on the use of the algorithm as well as clinical trials to identify potential correlations with other imaging modalities (such as CT-perfusion or MRI-PWI).
Further studies centered on the clinical validation of the algorithm will be prepared and proposed including larger study populations.
The assessment of the venous phase of collateral circulation (*Tong et al., 2018*) will remain a core subject for the next years and the implementation of the algorithm and its automatization will represent the main mid-term goals to achieve.

The project of the Thesis has also considered the recent innovations and the growing interest in the assessment of the dynamic profile of the collateral circulation and, in particular, of its venous phase.
The preliminary results of the current work generated enthousiasm in the team and other future PhD students as well as Master2 candidates showed an interest to continue the development of the algorithm.
Furthermore, other colleagues form other specialities, such as cardiologists and neurologists, manifested their interest in the further evolution of the algorithm.

7. REFERENCES (in alphabetical order)

Albers GW, Lansberg MG, Kemp S, Tsai JP, Lavori P, Christensen S, Mlynash M, Kim S, Hamilton S, Yeatts SD, Palesch Y, Bammer R, Broderick J, Marks MP. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). Int J Stroke. 2017 Oct;12(8):896-905. doi: 10.1177/1747493017701147. Epub 2017 Mar 24. PMID: 28946832; PMCID: PMC5916787.

Albers GW. Late Window Paradox. Stroke. 2018 Mar;49(3):768-771. doi: 10.1161/STROKEAHA.117.020200. Epub 2018 Jan 24. PMID: 29367336.

Anadani M, Finitsis S, Clarençon F, Richard S, Marnat G, Bourcier R, Sibon I, Dargazanli C, Arquizan C, Blanc R, et al. Collateral status reperfusion and outcomes after endovascular therapy: insight from the Endovascular Treatment in Ischemic Stroke (ETIS) Registry. J Neurointerv Surg. 2022;14:551-557.

Arsava EM, Vural A, Akpinar E, et al. The Detrimental Effect of Aging on Leptomenin-geal Collaterals in Ischemic Stroke. Journal of Stroke and Cerebrovascular Diseases 2014;23:421–6. doi:10.1016/j.jstrokecerebrovasdis.2013.03.014

Atkinson D, Hill DLG, Stoyle PNR, et al.: Automatic Compensation of Motion Artifacts in MRI. Magn Reson Med 1999; 41:163–170

Bang OY, Saver JL, Buck BH, Alger JR, Starkman S, Ovbiagele B, Kim D, Jahan R, Duckwiler GR, Yoon SR, Viñuela F, Liebeskind DS; UCLA Collateral Investigators. Impact of collateral flow on tissue fate in acute ischaemic stroke. J Neurol Neurosurg Psychiatry. 2008 Jun;79(6):625-9. doi: 10.1136/jnnp.2007.132100. Epub 2007 Dec 12. PMID: 18077482; PMCID: PMC2702489.

Bang OY, Saver JL, Kim SJ, et al. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. Stroke 2011;42:693–99.

Bederson JB, Germano IM, Guarino L. Cortical Blood Flow and Cerebral Perfusion Pressure in a New Noncraniotomy Model of Subarachnoid Hemorrhage in the Rat. Stroke 1995;26(6):1086-1091.

Ben Hassen W, Malley C, Boulouis G, Clarençon F, Bartolini B, Bourcier R, Rodriguez Régent C, Bricout N, Labeyrie MA, Gentric JC, Rouchaud A, Soize S, Saleme S, Raoult H, Gallas S, Eugène F, Anxionnat R, Herbreteau D, Bracard S, Naggara O. Inter- and intraobserver reliability for angiographic leptomeningeal collateral flow assessment by the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale. J Neurointerv Surg. 2019 Apr;11(4):338-341. doi: 10.1136/neurintsurg-2018-014185. Epub 2018 Aug 21. PMID: 30131382.

Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. 2021 Mar;6(1):I-LXII. doi: 10.1177/2396987321989865. Epub 2021 Feb 19. PMID: 33817340; PMCID: PMC7995316.

Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. N Engl J Med. janv 2015;372(1):11-20.

Broocks G, Kemmling A, Faizy T, McDonough R, Van Horn N, Bechstein M, Meyer L, Schön G, Nawabi J, Fiehler J, Kniep H, Hanning U. Effect of thrombectomy on oedema progression and clinical outcome in patients with a poor collateral profile. Stroke Vasc Neurol. 2021 Jun;6(2):222-229. doi: 10.1136/svn-2020-000570. Epub 2020 Nov 18. PMID: 33208492; PMCID: PMC8258058.

Campbell BC, Mitchell PJ, Kleinig TJ et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. N Engl J Med. 2015 Mar 12;372(11):1009-18.

Campbell BC. Clot Length Assessment in Stroke Therapy Decisions. Stroke. 2016 Mar;47(3):643-4. doi: 10.1161/STROKEAHA.115.012261. Epub 2016 Jan 14. PMID: 26768205.

Cao R, Ye G, Wang R, Xu L, Jiang Y, Wang G, Wang D, Chen J. Collateral Vessels on 4D CTA as a Predictor of Hemorrhage Transformation After Endovascular Treatments in Patients With Acute Ischemic Stroke: A Single-Center Study. Front Neurol. 2020 Feb 7;11:60. doi: 10.3389/fneur.2020.00060. PMID: 32117022; PMCID: PMC7019033.;

Carter PL, White WL, Atkinson JR. Regional Cortical Blood Flow at Craniotomy. Neurosurgery 1978;2(3):223–229.

Chevreul K, Durand-Zaleski I, Gouépo A, Fery-Lemonnier E, Hommel M, Woimant F. Cost of stroke in France. Eur J Neurol. juill 2013;20(7):1094-100.

Christoforidis GA, Saadat N, Kontzialis M, Karakasis CJ, Slivka AP. Predictors for the extent of pial collateral recruitment in acute ischemic stroke. Neuroradiol J. 2020 Apr;33(2):98-104. doi: 10.1177/1971400919897389. Epub 2020 Jan 2. PMID: 31896284; PMCID: PMC7140308.

Consoli A, Andersson T, Holmberg A et al. CT perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: the CAPRI study. J Neurointerv Surg. 2016 Dec;8(12):1211-1216.

Cortijo E, Calleja AI, García-Bermejo P, Mulero P, Pérez-Fernández S, Reyes J, Muñoz MF, Martínez-Galdámez M, Arenillas JF. Relative cerebral blood volume as a marker of durable tissue-at-risk viability in hyperacute ischemic stroke. Stroke. 2014 Jan;45(1):113-8. doi: 10.1161/STROKEAHA.113.003340. Epub 2013 Nov 26. PMID: 24281229.

Dargazanli C, Fahed R, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, Mazighi M, Consoli A, Piotin M, Lapergue B; ASTER Trial Investigators. Modified Thrombolysis in Cerebral Infarction 2C/Thrombolysis in Cerebral Infarction 3 Reperfusion Should Be the Aim of Mechanical Thrombectomy: Insights From the ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization). Stroke. 2018;49(5):1189-1196.

Faizy TD, Kabiri R, Christensen S, Mlynash M, Kuraitis G, Mader MM, Albers GW, Lansberg MG, Fiehler J, Wintermark M, et al. Association of Venous Outflow Profiles and Successful Vessel Reperfusion After Thrombectomy. *Neurology*. 2021;96:e2903–11.

Faizy TD, Kabiri R, Christensen S, Mlynash M, Kuraitis GM, Broocks G, Flottmann F, Marks MP, Lansberg MG, Albers GW, et al. Favorable Venous Outflow Profiles Correlate With Favorable Tissue-Level Collaterals and Clinical Outcome. *Stroke.* 2021;52:1761-1767.

Fandler-Höfler S, Heschl S, Argüelles-Delgado P, Kneihsl M, Hassler E, Magyar M, Kainz A, Berghold A, Niederkorn K, Deutschmann H, Fazekas F, Gattringer T. Single mean arterial blood pressure drops during stroke thrombectomy under general anaesthesia are associated with poor outcome. J Neurol. 2020 May;267(5):1331-1339. doi: 10.1007/s00415-020-09701-x. Epub 2020 Jan 18. PMID: 31955244; PMCID: PMC7184049.

Fery-Lemonnier E. La prévention et la prise en charge des accidents vasculaires cérébraux en France. 2009 Juin.

Fischer U, Kaesmacher J, Strbian D, Eker O, Cognard C, Plattner PS, Bütikofer L, Mordasini P, Deppeler S, Pereira VM, Albucher JF, Darcourt J, Bourcier R, Benoit G, Papagiannaki C, Ozkul-Wermester O, Sibolt G, Tiainen M, Gory B, Richard S, Liman J, Ernst MS, Boulanger M, Barbier C, Mechtouff L, Zhang L, Marnat G, Sibon I, Nikoubashman O, Reich A, Consoli A, Lapergue B, Ribo M, Tomasello A, Saleme S, Macian F, Moulin S, Pagano P, Saliou G, Carrera E, Janot K, Hernández-Pérez M, Pop R, Schiava LD, Luft AR, Piotin M, Gentric JC, Pikula A, Pfeilschifter W, Arnold M, Siddiqui AH, Froehler MT, Furlan AJ, Chapot R, Wiesmann M, Machi P, Diener HC, Kulcsar Z, Bonati LH, Bassetti CL, Mazighi M, Liebeskind DS, Saver JL, Gralla J; SWIFT DIRECT Collaborators. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet. 2022 Jul 9;400(10346):104-115. doi: 10.1016/S0140-6736(22)00537-2. PMID: 35810756.

Galinovic I, Kochova E, Khalil A, Villringer K, Piper SK, Fiebach JB. The ratio between cerebral blood flow and Tmax predicts the quality of collaterals in acute ischemic stroke. PLoS One. 2018;13(1):e0190811.

Ginsberg MD. The cerebral collateral circulation: Relevance to pathophysiology and treatment of stroke. Neuropharmacology. 2018 May 15;134(Pt B):280-292. doi: 10.1016/j.neuropharm.2017.08.003. Epub 2017 Aug 9. PMID: 28801174.

Goyal M, Demchuk AM, Menon BK et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015 Mar 12;372(11):1019-30.

Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731.

Hacke W, Kaste M, Bluhmki E et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008 Sep 25;359(13):1317-29.

Hao Y, Yang D, Wang H, Zi W, Zhang M, Geng Y, Zhou Z, Wang W, Xu H, Tian X, Lv P, Liu Y, Xiong Y, Liu X, Xu G; ACTUAL Investigators (Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry). Predictors for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of Acute Ischemic Stroke. Stroke. 2017 May;48(5):1203-1209. doi: 10.1161/STROKEAHA.116.016368. Epub 2017 Apr 3. PMID: 28373302.

Hartkamp MJ, van Der Grond J, van Everdingen KJ, Hillen B, Mali WP. Circle of Willis collateral flow investigated by magnetic resonance angiography. Stroke. 1999;30(12):2671–8.

Haute Autorité de Santé. Prise en charge précoce (alerte, phase pré-hospitalière, phase hospitalière initiale, indications de la thrombolyse) [Internet]. 2009 Mai p. 23. Disponible sur: http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-07/avc_prise_en_charge_precoce_-_recommandations.pdf.

Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke.* 2003;34:e109-37. Erratum in: *Stroke*. 2003;34(11):2774.

Hines ML, Morse T, Migliore M et al. ModelDB: A database to support computational neuroscience. Journal of Computational Neuroscience 2004;17(1):7-11.

Iadecola, C., Nedergaard, M. Glial regulation of the cerebral microvasculature. *Nat Neurosci* **10,** 1369–1376 (2007). https://doi.org/10.1038/nn2003.

Jovin TG, Chamorro A, Cobo E et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015 Jun 11;372(24):2296-306.

Jurczyszyn K, Osiecka BJ, Ziółkowski P. The use of fractal dimension analysis in estimation of blood vessels shape in transplantable mammary adenocarcinoma in Wistar rats after photodynamic therapy combined with cysteine protease inhibitors. Comput Math Methods Med. 2012;2012:793291. doi: 10.1155/2012/793291. Epub 2012 Sep 6. PMID: 22991578; PMCID: PMC3443606.

Khatri R, Rodriguez GJ, Suri MFK, Vazquez G, Ezzeddine MA. Leptomeningeal collateral response and computed tomographic perfusion mismatch in acute middle cerebral artery occlusion. J Vasc Interv Neurol. 2011;4(1):1–4.

Kim HJ, Lee SB, Choi JW, Jeon YS, Lee HJ, Park JJ, Kim EY, Kim IS, Lee TJ, Jung YJ, Ryu SY, Chun YI, Lee JS, Roh HG. Multiphase MR Angiography Collateral Map: Functional Outcome after Acute Anterior Circulation Ischemic Stroke. Radiology. 2020 Apr;295(1):192-201. doi: 10.1148/radiol.2020191712. Epub 2020 Feb 18. PMID: 32068506.

Kunz A, Iadecola C. Cerebral vascular dysregulation in the ischemic brain. *Handb Clin Neurol*. 2009;92:283-305. doi:10.1016/S0072-9752(08)01914-3.

Li C, Wu C, Wu L, Zhao W, Chen J, Ren M, Yao C, Yan X, Dong C, Song H, Ma Q, Duan J, Zhang Y, Zhang H, Jiao L, Wang Y, Jovin TG, Ji X; BAOCHE Investigators. Basilar Artery Occlusion Chinese Endovascular Trial: Protocol for a prospective randomized controlled study. Int J Stroke. 2022 Jul;17(6):694-697. doi: 10.1177/17474930211040923. Epub 2021 Aug 28. PMID: 34427475.

Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, Mazighi M, Consoli A, Piotin M; ASTER Trial Investigators. Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER Randomized Clinical Trial. JAMA. 2017 Aug 1;318(5):443-452. doi: 10.1001/jama.2017.9644. PMID: 28763550; PMCID: PMC5817613.

Lapergue B, Blanc R, Costalat V, Desal H, Saleme S, Spelle L, Marnat G, Shotar E, Eugene F, Mazighi M, Houdart E, Consoli A, Rodesch G, Bourcier R, Bracard S, Duhamel A, Ben Maacha M, Lopez D, Renaud N, Labreuche J, Gory B, Piotin M; ASTER2 Trial Investigators. Effect of Thrombectomy With Combined Contact Aspiration and Stent Retriever vs Stent Retriever Alone on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER2 Randomized Clinical Trial. JAMA. 2021 Sep 28;326(12):1158-1169. doi: 10.1001/jama.2021.13827. PMID: 34581737; PMCID: PMC8479584.

Lazzaro MA, Chen M, Christoforidis GA, Mohammad Y. The impact of diabetes on the extent of pial collaterals in acute ischemic stroke patients. J Neurointerv Surg. 2011 Sep;3(3):242-5. doi: 10.1136/jnis.2010.004507. Epub 2011 Feb 1. PMID: 21990833.

Leng X, Fang H, Leung TW, Mao C, Xu Y, Miao Z, Liu L, Wong KS, Liebeskind DS. Impact of Collateral Status on Successful Revascularization in Endovascular Treatment: A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2016;41(1-2):27-34. doi: 10.1159/000441803. Epub 2015 Nov 19. PMID: 26579719.

Liebeskind DS, Tomsick TA, Foster LD, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. Stroke 2014;45:759–64.

Liebeskind DS, Jahan R, Nogueira RG, et al; SWIFT Investigators. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. Stroke 2014;45:2036–40.

Liebeskind DS, Saber H, Xiang B, Jadhav AP, Jovin TG, Haussen DC, Budzik RF, Bonafe A, Bhuva P, Yavagal DR, Hanel RA, Ribo M, Cognard C, Sila C, Hassan AE, Smith WS, Saver JL, Nogueira RG; DAWN Investigators. Collateral Circulation in Thrombectomy for Stroke After 6 to 24 Hours in the DAWN Trial. Stroke. 2022 Mar;53(3):742-748. doi: 10.1161 STROKEAHA.121.034471. Epub 2021 Nov 3. PMID: 34727737.

Liggins JT, Mlynash M, Jovin TG, Straka M, Kemp S, Bammer R, et al: Interhospital variation in reperfusion rates following endovascular treatment for acute ischemic stroke. J Neurointerv Surg 2015; 7: 231–233.

Liu D, Nie X, Pan Y, Yan H, Pu Y, Wei Y, Cai Y, Ding Y, Lu Q, Zhang Z, Gu W, Hou X, Yang Z, Wen M, Wang P, Ma G, Ma N, Miao Z, Leng X, Yan B, Davis SM, Wang Y, Liu L. Adverse Outcomes Associated With Higher Mean Blood Pressure and Greater Blood Pressure Variability Immediately After Successful Embolectomy in Those With Acute Ischemic Stroke, and the Influence of Pretreatment Collateral Circulation Status. J Am Heart Assoc. 2021 Feb;10(5):e019350. doi: 10.1161/JAHA.120.019350. Epub 2021 Feb 26. PMID: 33634704; PMCID: PMC8174261.

Mainster MA. The fractal properties of retinal vessels: embryological and clinical implications. Eye (Lond). 1990;4 (Pt 1):235-41. doi: 10.1038/eye.1990.33. PMID: 2323476.

Majumdar S, Lin J, Link T, Millard J, Augat P, Ouyang X, Newitt D, Gould R, Kothari M, Genant H. Fractal analysis of radiographs: assessment of trabecular bone structure and prediction of elastic modulus and strength. Med Phys. 1999 Jul;26(7):1330-40. doi: 10.1118/1.598628. PMID: 10435535.

Mangiafico S, Consoli A, Renieri L et al. Semi-quantitative and qualitative evaluation of pial leptomeningeal collateral circulation in acute ischemic stroke of the anterior circulation: the Careggi Collateral Score. Ital J Anat Embryol. 2013;118(3):277-87.

Mangiafico S, Saia V, Nencini P, Romani I, Palumbo V, Pracucci G, Consoli A, Rosi A, Renieri L, Nappini S, Limbucci N, Inzitari D, Gensini GF. Effect of the Interaction between Recanalization

and Collateral Circulation on Functional Outcome in Acute Ischaemic Stroke. Interv Neuroradiol. 2014 Dec;20(6):704-14.

McVerry F, Liebeskind DS, Muir KW. Systematic review of methods for assessing leptomeningeal collateral flow. AJNR Am J Neuroradiol. 2012 Mar;33(3):576-82. doi: 10.3174/ajnr.A2794. Epub 2011 Dec 1. PMID: 22135128; PMCID: PMC7966447.

Menon BK. Neuroimaging in Acute Stroke. Continuum (Minneap Minn). 2020 Apr;26(2):287-309. doi: 10.1212/CON.0000000000000839. PMID: 32224753.

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 May;275(2):510-20.

Menon BK, O'Brien B, Bivard A. et al. Assessment of leptomeningeal collaterals using dynamic CT angiography in patients with acute ischemic stroke. J Cereb Blood Flow Metab 2013; 33: 365-371.

Muehlen I, Kloska SP, Gölitz et al. Noninvasive Collateral Flow Velocity Imaging in Acute Ischemic Stroke: Intraindividual Comparison of 4D-CT Angiography with Digital Subtraction Angiography. Rofo Jan 21 2019 (efirst).

Mohammaden MH, Haussen DC, Pisani L, Al-Bayati AR, Bhatt NR, Jillella DV, Bianchi NA, Belagaje SR, Frankel MR, Nogueira RG. Characterizing Fast and Slow Progressors in Anterior Circulation Large Vessel Occlusion Strokes. Interv Neuroradiol. 2022 Apr 5:15910199221083100. doi: 10.1177/15910199221083100. Epub ahead of print. PMID: 35379038.

Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG; DAWN Trial Investigators. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018 Jan 4;378(1):11-21. doi: 10.1056/NEJMoa1706442. Epub 2017 Nov 11. PMID: 29129157.

Qian J, Fan L, Zhang W, et al. A meta-analysis of collateral status and outcomes of mechanical thrombectomy. Acta Neurol Scand 2020;142:191–9. doi:10.1111/ane.13255

Pfaff JAR, Schönenberger S, Herweh C, Ulfert C, Nagel S, Ringleb PA, Bendszus M, Möhlenbruch MA. Direct Transfer to Angio-Suite Versus Computed Tomography-Transit in Patients Receiving Mechanical Thrombectomy: A Randomized Trial. *Stroke*. 2020;51:2630-2638.

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. 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 Dec;50(12):e344-e418. doi: 10.1161/STR.0000000000000211. Epub 2019 Oct 30. Erratum in: Stroke. 2019 Dec;50(12):e440-e441. PMID: 31662037.

Raychev R, Liebeskind DS, Yoo AJ, Rasmussen M, Arnaudov D, Brown S, Saver J, Simonsen CZ. Physiologic predictors of collateral circulation and infarct growth during anesthesia - Detailed analyses of the GOLIATH trial. J Cereb Blood Flow Metab. 2020 Jun;40(6):1203-1212. doi: 10.1177/0271678X19865219. Epub 2019 Aug 1. PMID: 31366300; PMCID: PMC7238375.

Requena M, Olivé-Gadea M, Muchada M, Hernández D, Rubiera M, Boned S, Piñana C, Deck M, García-Tornel Á, Díaz-Silva H, et al. Direct to Angiography Suite Without Stopping for Computed Tomography Imaging for Patients With Acute Stroke: A Randomized Clinical Trial. *JAMA Neurol*. 2021;78:1099-1107.

Ribo M, Flores A, Rubiera M, et al. Extending the time window for endovascular procedures according to collateral pial circulation. Stroke 2011;42:3465–9.

Riou-Comte N, Zhu F, Cherifi A, Richard S, Nace L, Audibert G, Achit H, Costalat V, Arquizan C, Beaufils O, Consoli A, Lapergue B, Loeb T, Rouchaud A, Macian F, Cailloce D, Biondi A, Moulin T, Desmettre T, Marnat G, Sibon I, Combes X, Lebedinsky AP, Vuillemet F, Kempf N, Pierot L, Moulin S, Lemmel P, Mazighi M, Blanc R, Sabben C, Schluck E, Bracard S, Anxionnat R, Guillemin F, Hossu G, Gory B; DIRECT ANGIO Investigators. Direct transfer to angiosuite for patients with severe acute stroke treated with thrombectomy: the multicentre randomised controlled DIRECT ANGIO trial protocol. BMJ Open. 2021 Mar 15;11(3):e040522. doi: 10.1136/bmjopen-2020-040522. PMID: 33722864; PMCID: PMC7970280.

Rocha M, Jovin TG. Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke: Clinical and Research Implications. Stroke. 2017 Sep;48(9):2621-2627. doi: 10.1161/STROKEAHA.117.017673. Epub 2017 Aug 9. PMID: 28794271.

Saver JL, Goyal M, Bonafe A et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015 Jun 11;372(24):2285-95.

Schönenberg S, Uhlmann L, Hacke W et al. Effect of Conscious Sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing end-vascular thrombectomy: a randomized clinical trial. JAMA, 2016; 316(19):1986-96.

Seners P, Caroff J, Chausson N, Turc G, Denier C, Piotin M, Aghasaryan M, Alecu C, Chassin O, Lapergue B, Naggara O, Ferrigno M, Arquizan C, Cho TH, Narata AP, Richard S, Bricout N, Mazighi M, Costalat V, Gory B, Debiais S, Consoli A, Bracard S, Oppenheim C, Mas JL, Smadja D, Spelle L, Baron JC; PREDICT-RECANAL collaborators. Recanalization before Thrombectomy in Tenecteplase vs. Alteplase-Treated Drip-and-Ship Patients. J Stroke. 2019 Jan;21(1):105-107. doi: 10.5853/jos.2018.01998. Epub 2018 Dec 18. PMID: 30558399; PMCID: PMC6372902.

Seners P, Roca P, Legrand L, Turc G, Cottier JP, Cho TH, Arquizan C, Bracard S, Ozsancak C, Ben Hassen W, Naggara O, Lion S, Debiais S, Berthezene Y, Costalat V, Richard S, Magni C, Mas JL, Baron JC, Oppenheim C. Better Collaterals Are Independently Associated With Post-Thrombolysis Recanalization Before Thrombectomy. Stroke. 2019 Apr;50(4):867-872. doi: 10.1161/STROKEAHA.118.022815. PMID: 30908160.

Seyman E, Shaim H, Shenhar-Tsarfaty S, Jonash-Kimchi T, Bornstein NM, Hallevi H. The collateral circulation determines cortical infarct volume in anterior circulation ischemic stroke. BMC Neurol. 2016;16(1):206.

Simonsen CZ, Yoo AJ, Leif H et al. Effect of general anesthesia and conscious sedation during endvascular therapy on infarct growth and clinical outcomes in acute ischemic stroke. A randomized controlled trial. JAMA 2018;75(4):470-7.

Singh N, Bala F, Kim BJ, Najm M, Ahn SH, Fainardi E, Rubiera M, Khaw AV, Zini A, Goyal M, et al. Time-resolved assessment of cortical venous drainage on multiphase CT angiography in patients with acute ischemic stroke. *Neuroradiology.* 2022;64:897-903.

Smit EJ, Vonken EJ, van Seeters T. et al. Timing-invariant imaging of collateral vessels in acute ischemic stroke. Stroke 2013; 44: 2194-2199 . doi:10.1161/STROKEAHA.111.000675.

Tao C, Li R, Zhu Y, Qun S, Xu P, Wang L, Zhang C, Liu T, Song J, Sun W, Wang G, Baxter B, Qureshi A, Liu X, Nogueira RG, Hu W. Endovascular treatment for acute basilar artery occlusion: A multicenter randomized controlled trial (ATTENTION). Int J Stroke. 2022 Aug;17(7):815-819. doi: 10.1177/17474930221077164. Epub 2022 Feb 22. PMID: 35102797.

Thierfelder KM, Havla L, Beyer S. et al. Color-coded cerebral computed tomographic angiography-Implementation of a convolution-based algorithm and first clinical evaluation in patients with acute ischemic stroke. Invest Radiol 2015; 50: 361-365.

Tong LS, Guo ZN, Ou YB, Yu YN, Zhang XC, Tang J, Zhang JH, Lou M. Cerebral venous collaterals: A new fort for fighting ischemic stroke? *Prog Neurobiol.* 2018;163-164:172-193.

Turk AS 3rd, Siddiqui A, Fifi JT, De Leacy RA, Fiorella DJ, Gu E, Levy EI, Snyder KV, Hanel RA, Aghaebrahim A, Woodward BK, Hixson HR, Chaudry MI, Spiotta AM, Rai AT, Frei D, Almandoz JED, Kelly M, Arthur A, Baxter B, English J, Linfante I, Fargen KM, Mocco J. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion

(COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial. Lancet. 2019 Mar 9;393(10175):998-1008. doi: 10.1016/S0140-6736(19)30297-1. PMID: 30860055.

Udupa JK, Saha PK. Fuzzy Connectedness and Image Segmentation. Proceedings of the IEEE, 2003. 91(10):1649-69.

van Horn N, Kniep H, Leischner H, McDonough R, Deb-Chatterji M, Broocks G, Thomalla G, Brekenfeld C, Fiehler J, Hanning U, et al. Predictors of poor clinical outcome despite complete re-perfusion in acute ischemic stroke patients. *J Neurointerv Surg.* 2021;13:14-18.

Vasquez, HE, Murlimanju, BV, Shrivastava, A *et al.* Intracranial collateral circulation and its role in neurovascular pathology. *Egypt J Neurosurg* **36,** 2 (2021). https://doi.org/10.1186/s41984-020-00095-6.

Yushkevich PA, Piven J, Hazlett HC et al. USse-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage, 2006 Jul 1;31(3):1116-28.

8. SUMMARY OF THE PHD THESIS

French

L'objet de cette thèse est centré sur l'évaluation de la circulation collatérale chez les patients présentant un accident vasculaire cérébral ischémique (AVCi). Le rôle de cette circulation collatérale a été investigué dans la littérature alors que les caractéristiques hémodynamiques restent encore peu connues. Depuis 2018 on a pu observer un intérêt croissant autour de la circulation collatérale et plusieurs équipes dans le monde ont concentré leurs efforts dans la compréhension de la physiopathologie des AVCi ainsi que dans des nouvelles méthodes d'imagerie pour décrire de manière plus détaillée le fonctionnement hémodynamique de la circulation collatérale.

Les objectifs de la thèse ont été développés sur trois axes distincts : (i) *l'analyse de l'impact clinique* de la circulation collatérale dans les accidents vasculaires cérébraux ischémiques, (ii) *l'analyse critique de l'évaluation de la circulation collatérale par artériographie cérébrale* et le (iii) *développement d'un algorithme de caractérisation de la circulation collatérale* applicable en temps réel aux images artériographiques.

L'impact clinique de la circulation collatérale représente une étape essentielle dans la compréhension physiopathologique. Plusieurs études ont mis en évidence des corrélations significatives entre une bonne circulation collatérale et les résultats cliniques favorables et les patients avec une bonne circulation collatérale sont considérés comme les meilleurs candidats pour les procédures de thrombectomie mécanique. Dans cette thèse je présente les résultats d'une étude rétrospective d'analyse clinique (étude UNCLOSE), ciblée sur ce sous-groupe spécifique de patients présentant un AVCi et une bonne circulation collatérale évaluée par artériographie cérébrale (échelle ASITN/SIR) et traités par thrombectomie mécanique. Les conclusions de cette étude ont mis en évidence un résultat clinique défavorable dans presque la moitié de ce sous-groupe (47%) malgré la présence d'une bonne circulation collatérale. Les facteurs qui peuvent expliquer ce type de résultats ne différent pas de ceux déjà décrit chez les patients avec une collatéralité insuffisante ou absente, avec l'exception de l'absence de significativité du First Pass Effect et un rôle protectif de la thrombolyse intraveineuse. En outre, ces résultats posent l'accent sur la modalité d'évaluation de la circulation collatérale par artériographie cérébrale et la nécessité de proposer d'autres paramètres d'évaluation.

Un nouveau paramètre d'évaluation a été décrit tout en proposant une **analyse critique de l'évaluation artériographique de la circulation collatérale** : la phase veineuse artériographique de la collatéralité (CVP, collateral venous phase). Je présente les résultats d'une étude rétrospective d'éva-

luation artériographique de la présence d'une phase veineuse collatérale en rapport avec l'efficacité de la circulation collatérale (évaluation qualitative). Ce type de paramètre représente l'interprétation physiopathologique du rôle du système veineux et venulaire de la circulation collatérale dans le maintien de la perfusion cérébrale pendant l'occlusion artérielle et l'évolution de l'ischémie cérébrale. Le CVP a été comparé à l'évaluation faite par l'échelle ASITN/SIR et le CVP seul ainsi que l'évaluation composite de ces deux paramètres ont montré des meilleurs résultats en termes de corrélation avec les résultats cliniques.

La dernière partie de la thèse est centrée sur le **développement d'un algorithme de caractérisation de la circulation collatérale** (algorithme ASCOT). L'algorithme permettra d'analyser en temps réel les images d'artériographie cérébrale en cours de traitement par thrombectomie mécanique et de fournir des données d'efficacité de la circulation collatérale qui pourront aider à élargir les connaissances physiopathologiques sur les AVCi, orienter les choix thérapeutiques intra-procédurales et de prise en charge post-procédurale.

English

The focus of this thesis is on the evaluation of collateral circulation in patients with acute ischemic stroke (AIS). The role of this collateral circulation has been investigated in the literature while the hemodynamic characteristics are still little known. Since 2018 there has been a growing interest around collateral circulation and several teams around the world have focused their efforts on understanding the pathophysiology of AIS as well as on new imaging methods to further describe the hemodynamic functioning of the collateral circulation.

The objectives of the thesis were developed on three distinct axes: (i) *the analysis of the clinical impact* of collateral circulation in ischemic stroke, (ii) *the critical analysis of collateral circulation assessment by cerebral angiography* and (iii) *the development of a real-time collateral circulation characterization algorithm* for angiographic images.

The clinical impact of collateral circulation is an essential step in the pathophysiological understanding. Several studies have shown significant correlations between good collateral circulation and favorable clinical outcomes and patients with good collateral circulation are considered the best candidates for mechanical thrombectomy procedures. In this thesis I present the results of a retrospective clinical analysis study (UNCLOSE study), targeted on this specific subgroup of patients with AIS and good collateral circulation evaluated by cerebral arteriography (ASITN/SIR scale) and

treated by mechanical thrombectomy. The findings of this study showed an adverse clinical outcome in almost half of this subgroup (47%) despite the presence of good collateral circulation. The factors that may explain this type of results are not different from those already described in patients with insufficient or absent collaterals, with the exception of the lack of significance of First Pass Effect and a protective role of intravenous thrombolysis. In addition, these results focus on the modality of evaluation of collateral circulation by cerebral arteriography and the need to propose other evaluation parameters.

A new evaluation parameter was described while proposing **a critical analysis of the angiographical evaluation of collateral circulation**: the angiographical venous phase of collateral (CVP, collateral venous phase). I present the results of a retrospective study of angiographic evaluation of the presence of a collateral venous phase in relation to the collateral circulation efficiency (qualitative evaluation). This type of parameter represents the physiopathological interpretation of the role of the venous and venular system of collateral circulation in maintaining cerebral perfusion during arterial occlusion and progression of cerebral ischemia. The CVP was compared to the ASITN/SIR assessment and the CVP alone and the composite assessment of these two parameters showed better results in terms of correlation with clinical results.

The last part of the thesis focuses on the **development of a collateral circulation characterization algorithm** (ASCOT). The algorithm will enable real-time analysis of brain angiography images acquired during mechanical thrombectomy procedures and provide data about collateral circulation effectiveness that could help expand pathophysiology knowledge on AIS, and drive intraprocedural and post-procedural treatment choices.