Early Transcranial Color-Coded Sonography as a predictor of Hemorrhagic Transformation after Thrombectomy

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Abbreviations

AIS: Acute Ischemic Stroke

BBB: Blood-brain barrier

CHS: Cerebral hyperperfusion syndrome

CI: Confidence Interval

CT: Computed Tomography

ECASS: European Cooperative Acute Stroke Study

EDV: End-diastolic velocities

HT: Hemorrhagic Transformation

IV rtPA: Intravenous recombinant tissue plasminogen activator

LVO: Large vessel occlusion

MCA: Middle cerebral artery

MCAsRo: Ratio of the mean flow velocities of middle cerebral artery

MFV: Mean flow velocities

MRI: Magnetic resonance imaging

mRS: modified Rankin Scale

MT: Mechanical Thrombectomy

mTICI: modified Treatment in Cerebral Ischemia

NIHSS: National Institute of Health Stroke Scale

OR: Odds Ratio

PH: Parenchymal Hematoma

PSV: Peak systolic velocities

SD: Standard Deviation

TCCS: Transcranial color-coded sonography

Abstract

Background and Purpose: Endovascular therapies have achieved high reperfusion rates and excellent clinical outcomes, however it may cause reperfusion injury that can lead to hemorrhagic transformation (HT). Transcranial color-coded sonography (TCCS) is a valid diagnostic tool that can be used to assess cerebrovascular disease. We aimed to determine the predictive value of early TCCS on HT after successful endovascular therapy in acute ischemic stroke due to large vessel occlusion.

Methods: We retrospectively evaluated a cohort of consecutive patients with large vessel occlusion strokes submitted to mechanical thrombectomy (MT) that performed TCCS within the first 24 hours after symptoms onset. Recanalization was assessed in the final angiogram after thrombectomy. We measured flow velocities in asymptomatic and symptomatic middle cerebral artery (MCA). Mean flow velocities (MFV) of the MCAs and ratio of the MFV of MCAs (MCAsRo) were calculated. Head CT scan was performed at 24 hours post stroke onset. All scans were reviewed by a neuroradiologist unaware of clinical events and any parenchymal hematoma (PH1 or PH2) was considered HT. Univariate associations and multivariate analyses were used to identify early independent predictors for HT and 3-month mRS among TCCS findings.

Results: We included 101 patients; mean age was 68.95 (SD, 12.70) years. A total of 74 (73.30%) patients underwent intravenous thrombolysis followed by MT. MCAsRo was significantly higher in patients with HT. In a multivariate analysis, adjusting for age, MCAsRo remained an independent predictor of HT (odds ratio, 6.890; 95% confidence interval, 1.332-35.643; P=0.021).

Conclusion: Early MCAsRo TCCS assessment is an independent predictor of HT and may be useful in promoting preventive interventions.

Key-Words: stroke; reperfusion injury; thrombectomy; ultrasonography; middle cerebral artery

Resumo

Introdução: Terapêuticas endovasculares têm alcançado taxas de reperfusão altas e resultados clínicos excelentes, contudo podem causar lesão de reperfusão, que por sua vez está na origem da ocorrência de transformação hemorrágica (TH). O Doppler transcraniano codificado a cores (DTCC) é uma ferramenta diagnóstica válida utilizada na patologia cerebrovascular. Foi nosso objetivo avaliar a capacidade preditora de transformação hemorrágica da realização de DTCC precoce em doentes submetidos a trombectomia e recanalizados devido a um acidente vascular cerebral isquémico (AVCi) com oclusão de grande vaso.

Métodos: Num estudo de coorte histórica foram incluídos casos com AVCi devido a oclusão de grande vaso submetidos a trombectomia mecânica (TM) que realizaram DTCC nas primeiras 24 horas após início dos sintomas. Recanalização foi definida no angiograma final após TM. A realização do DTCC ocorreu nas primeiras 24 horas após início dos sintomas. Foram colhidas as velocidades na artéria cerebral média (ACM) sintomática e assintomática. As velocidades médias (VM) das ACMs foram quantificadas bem como o rácio da ACM sintomática/assintomática (RaACMs). Realizaram-se TAC Crânio-Encefálicas (CE) às 24 horas após instalação sintomática. Todas as TAC-CE foram revistas por neurorradiologista cego para informação clínica e hemodinâmica e foi considerada TH qualquer hematoma parenquimatoso (PH1 ou PH2). A identificação de preditores independentes precoces de TH tendo em conta os dados do DTCC compreendeu comparações univariáveis e análises multivariáveis.

Resultados: Foram incluídos 101 doentes, com idade média de 68.95 (DP, 12.70) anos. Um total de 74 doentes foram submetidos a fibrinólise endovenosa seguida de TM. RaACMs foi estatisticamente superior nos doentes com TH. Em análise multivariável ajustada para a idade, o RaACMs manteve-se um preditor independente de TH (odds ratio, 6.890; intervalo de confiança, 1.332-35.643; P=0.021).

Conclusão: O RaACMs avaliado precocemente por DTCC é um preditor independente de TH que pode ser útil na implementação de medidas preventivas.

Palavras-chave: acidente vascular cerebral; lesão de reperfusão; trombectomia; ultrassonografia; artéria cerebral média

Introduction

Endovascular therapies, such as mechanical thrombectomy (MT), with last generation devices (such as stent retrievers) have revolutionized the treatment of acute ischemic stroke (AIS) due to large vessel occlusion (LVO). Recently published randomized clinical trials and subsequent meta-analyses have shown its efficacy and safety with higher reperfusion rates and better clinical outcomes, respectively, when compared to medical management alone with intravenous recombinant tissue plasminogen activator (IV rtPA).[1-8] Moreover, recent studies confirmed the efficacy and safety of MT in routine clinical practice.[9-11]

Nonetheless, reperfusion of ischemic brain may have a deleterious effect on reperfused territory and cause reperfusion injury through several mechanisms.[12,13] Hemorrhagic transformation (HT) is a common and feared complication of MT, which has been associated with poor clinical outcome.[14,15] Data from previous studies have also proposed predictors and risk factors of HT in patients treated with MT, such as atrial fibrillation, diabetes mellitus, longer symptom onset to treatment intervals, wake-up strokes, and Asian race.[14-16] However, the ability to predict this event in useful time in order to avoid the clinical deterioration of the patients is still missing.

Transcranial color-coded sonography (TCCS) as a non-invasive, bedside and reliable method for the evaluation of cerebral hemodynamics in AIS is a diagnostic tool that can be used to early assess intracranial status. It can identify stroke complications and differentiate intracerebral hemorrhage from ischemic stroke, monitor the efficiency of reperfusion therapies and provide information on patients' prognosis in AIS.[17-20]

The aim of this study is to determine the predictive value of early TCCS on HT in patients submitted to MT and reperfused with LVO strokes in the anterior circulation.

Methods

Study Population

We included consecutive patients with AIS admitted at our tertiary, university hospital in Portugal, from January 2015 to September 2017 in a historic cohort study. Patients were treated with IV rtPA followed by MT or endovascular treatment alone up to 6 hours after symptoms onset. The exclusion criteria were as follows: AIS involving the posterior circulation; patients submitted to MT alone or MT plus IV rtPA who were not reperfused; unavailable information about reperfusion state; and TCCS was not performed after the reperfusion procedure and in the first 24 hours after the onset of AIS or with insufficient acoustic bone window. The algorithm for patient inclusion is presented in Figure 1.

We collected vascular risk factors from a standardized local clinical registry. Considering the observational and retrospective nature of the study, written informed consent was waived. Ethics approval was obtained from the local institutional review board.

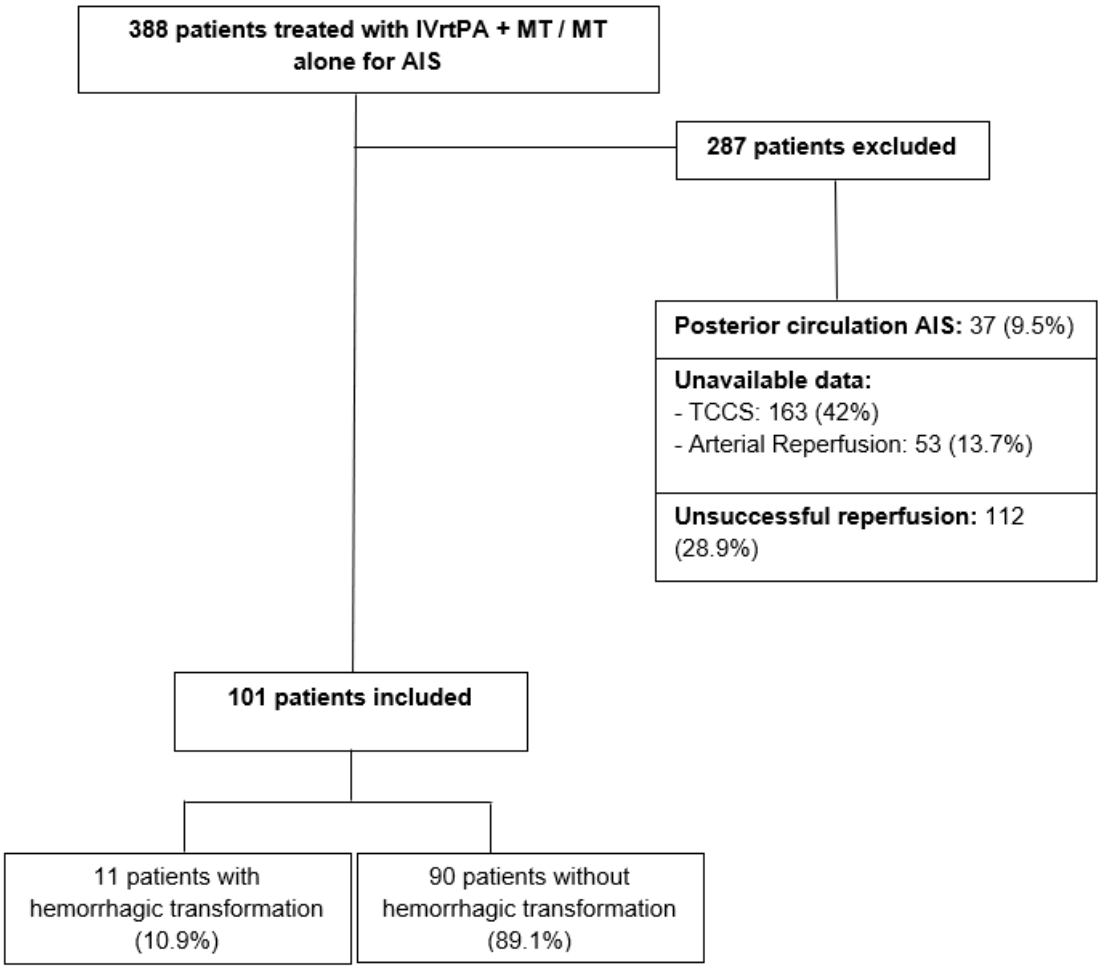

Figure 1. Algorithm for patient inclusion. All exclusion criteria and the respective number of patients are listed. AIS indicates acute ischemic stroke; IVrtPA, intravenous recombinant tissue plasminogen activator; MT, mechanical thrombectomy; and TCCS, transcranial color-coded sonography.

Data Collection

We collected data on patients' vascular risk factors from a prospectively defined clinical registry: age, gender, smoking, alcoholism, peripheral artery disease, arterial hypertension, atrial fibrillation, coronary artery disease, congestive heart failure, dyslipidemia, obesity, diabetes mellitus. National Institutes of Health Stroke Scale (NIHSS) score on admission and at discharge were graded by a vascular neurologist.

Endovascular Procedures

All enrolled patients on admission were submitted to a noncontrast head computed tomography (CT) and CT angiography. CT scan equipment used was General Electric Lightspeed (64x). All patients were treated with IVrtPA followed by endovascular therapy or MT alone within 6 hours after stroke symptoms onset. MT was performed with a stent retriever or aspiration device at the discretion of the attending neuroradiologist. Arterial reperfusion was

assessed by the angiographic pattern at the end of endovascular procedure and successful reperfusion was considered as grade 2b or 3 from the modified Treatment in Cerebral Ischemia (mTICI).[21]

Neuroimaging and Clinical Outcome Assessment

TCCS (General Electrics Logiq 7 with a 3-Mhz sector probe) examination was performed within the first 24 hours after symptoms onset by experienced vascular neurologists through the transtemporal bone window. We measured angle-corrected peak systolic velocities and end-diastolic velocities (PSV and EDV, in cm/s) of the symptomatic and asymptomatic MCA. Pulsatility index (PI) of the right and left MCA was also measured. Mean flow velocities of the symptomatic and asymptomatic MCA (MFV, in cm/s), and MFV of the symptomatic MCA/MFV of the asymptomatic MCA ratio (MCAsRo) were calculated.

Head CT scan was performed 24 hours after symptoms onset. All scans were reviewed by a neuroradiologist who was blinded to the clinical information and hemodynamic status. HT was diagnosed and classified according to European Cooperative Acute Stroke Study (ECASS) III trial[22] definitions. Any parenchymal hematoma (PH1 or PH2) was considered HT. At admission we evaluated neurological status through NIHSS score. To estimate 3-month clinical outcome we used mRS score usually obtained from the follow-up appointment registry or, when missing, by telephone contact with the patient or relative.[23]

Statistical Methodology

Quantitative variables are described as mean and standard deviation and qualitative variables as frequency (percentage). Univariate associations with MFV of the symptomatic MCA were assessed using a linear regression and presented as β (95% confidence interval).

Independent predictors of HT and 3-month functional outcome were determined using a binary logistic regression and ordinal regression, respectively. The variables included in the multivariate analyses for predictors of HT and 3-month mRS were the MFV of the symptomatic MCA and MCAsRo adjusting for age or for age and NIHSS at admission, respectively.

A *P* value<0,05 was considered statistically significant. All the statistical tests were made using IBM SPSS Statistics software, version 24.

Table 1. Baseline Characteristics of the Study and Univariate Linear Regression for Predictors of MFV of the symptomatic MCA

Variable	Total Population, n=101 Patients	Univariate Association with MFV of the symptomatic MCA, β (95% CI)	*P* Value
Age, y, mean±SD	67.99±13.86	-0.348 (-0.779 to -0.234)	<0.001
Male gender, n (%)	59 (41.60)	0.150 (-1.940 to 14.149)	0.135
Smoking, n (%)	15 (14.90)	0.105 (-0.019 to 0.062)	0.298
Alcoholism, n (%)	11 (10.90)	0.104 (-0.019 to 0.061)	0.300
Hypertension, n (%)	60 (59.40)	0.104 (-0.019 to 0.061)	0.302
Diabetes mellitus, n (%)	19 (18.80)	0.103 (-0.019 to 0.061)	0.303
Dyslipidemia, n (%)	45 (44.60)	0.103 (-0.019 to 0.061)	0.306
Atrial fibrillation, n (%)	31 (30.70)	0.103 (-0.019 to 0.061)	0.305
Heart failure, n (%)	11 (10.90)	0.104 (-0.019 to 0.061)	0.302
Coronary artery disease, n (%)	11 (10.90)	0.104 (-0.019 to 0.061)	0.303
Previous mRS, mean±SD	0.36±0.74	-0.068 (-7.460 to 3.697)	0.505
NIHSS at admission, mean±SD	16.42±6.25	-0.092 (-0.971 to 0.393)	0.401
Fibrinolysis (IV), n (%)	74 (73.30)	0.151 (-2.083 to 15.830)	0.131
Time from symptom onset to thrombectomy, min, mean±SD	259.81±130.39	0.090 (-0.019 to 0.047)	0.401

Dichotomous variables are presented as frequency (%). CI indicates confidence interval; SD, standard deviation; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MFV, mean flow velocity; and MCA, middle cerebral artery.

Results

During the study period, a total of 388 patients were submitted to MT in our tertiary university hospital in Portugal. Of those, 287 patients were excluded due to unsuccessful reperfusion (112, 28.9%), unavailable data about TCCS (163, 42%) or arterial reperfusion (53, 13.7%), and/or posterior circulation strokes (37, 9.5%). For our analysis, we have included 101 patients: mean age was 68.95±12.70 years, and 58 (57.50%) were men. Baseline features, including information on demographics, medical history, clinical parameters and AIS therapies, are presented in Table 1. A total of 74 (73.30%) patients underwent IVrtPA as a bridging strategy and 27 (26.70%) MT alone.

The MFV in the symptomatic MCA was 59,70±20.92 cm/s and 61.92±26.12 cm/s in the asymptomatic MCA. The MCAsRo ranged from 0.44 to 1.84 (mean 1.02±0.34). Postinterventional head CT scan performed 24 hours after symptoms onset showed HT in 11 patients (10.9%). Of those, 7 patients (6.9%) had a PH2. On TCCS, the MFV of the symptomatic MCA was not statistically different between HT and non-HT patients (66.43±11.17 cm/s vs 58.78±20.93 cm/s, *P*=0.24), whereas the MCAsRo was significantly higher in HT group when compared to the non-HT group (1.32±0.39 vs 1.02±0.34, *P*=0.01) (Figure 2). In multivariate analyses, adjusting for age, MCAsRo remained an independent predictor of HT, though neither MFV of the symptomatic MCA nor MCAsRo were independent predictors of 3-month mRS (odds ratio, 6.890; 95% confidence interval, 1.332-35.643; *P*=0.021, Table 2).

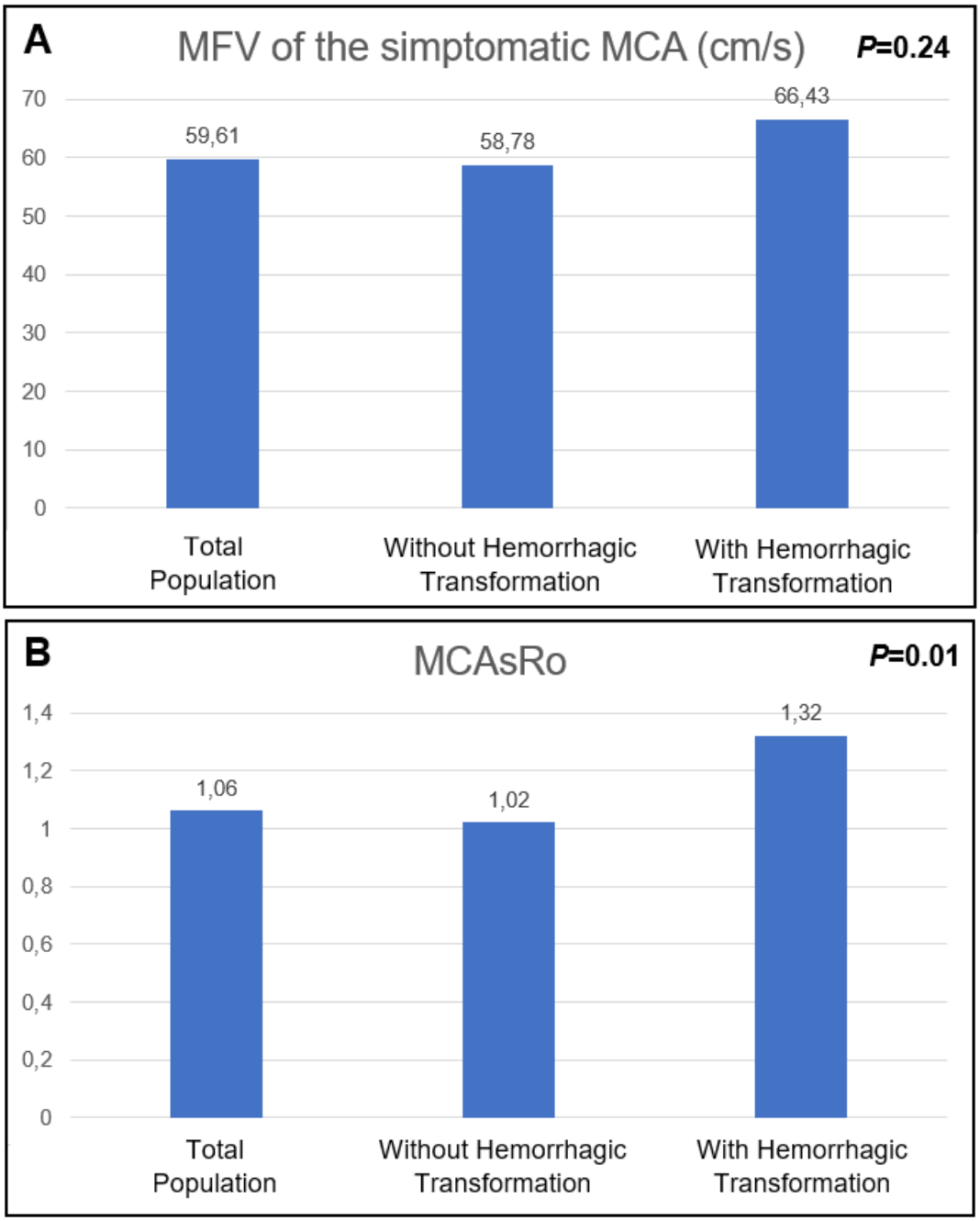

Figure 2. Absolute values of mean flow velocity (MFV) of the symptomatic middle cerebral artery (MCA) and ratio of the MFV of MCAs (MCAsRo) in total population, patients with hemorrhagic transformation (HT) and patients without HT. **A,** MFV of the symptomatic MCA. **B,** MCAsRo.

Table 2. Independent association of MFV of the symptomatic MCA and MCAsRo with HT and 3-month mRS using a binary logistic regression and ordinal regression, respectively

Predictors of HT	OR (95% CI)	*P* value
MFV of the symptomatic MCA	1.032 (0.997-1.068)	0.071
MCAsRo	6.890 (1.332-35.643)	0.021
Predictors of 3-month mRS	β (95% CI)	*P* value
MFV of the symptomatic MCA	0.000 (-0.021 to 0.020)	0.969
MCAsRo	-0.341 (-1.364 to 0.682)	0.513

OR (95% CI) and associated *P* values represent the results of binary logistic regression, and β (95% CI) and associated P values represent the results of ordinal regression. The multivariate model for predictors of HT is adjusted for age while the model for predictors of 3-month mRS is adjusted for age and baseline National Institute of Health Stroke Scale. CI indicates confidence interval; OR, odds ratio; HT, hemorrhagic transformation; MFV, mean flow velocity; MCA, middle cerebral artery; MCAsRo, MFV of the symptomatic MCA/MFV of the asymptomatic MCA ratio; and mRS, modified Rankin Scale.

Discussion

The main finding of our study is that early MCAsRo assessed by TCCS is an independent predictor of HT in AIS patients successfully treated for anterior circulation LVO by endovascular therapy.

The clinical features of our study population are similar to other published acute stroke cohorts. More than half of the patients were diagnosed with arterial hypertension, about half of the population had dyslipidemia. About one third showed atrial fibrillation which appeared to be a risk factor of HT in patients who underwent MT.[14] Lower MFVs of the symptomatic MCA were associated with older age. Considering the age dependence of the flow velocities in the basal cerebral arteries demonstrated in previous studies, this association was expected.[24,25]

Bedside TCCS examination showed no statistically significant difference in the MFV of the symptomatic MCA between HT and non-HT patients. This result can be attributed to the interindividual variability in blood flow velocities or to confounding factors that may influence individual MFV, for instance the patients' age. On the other hand, MCAsRo showed to be an independent predictor of post-thrombectomy HT with the highest MCAsRo in this group. Our TCCS findings demonstrate that focal cerebral hyperperfusion after a successful endovascular therapy for LVO strokes in anterior circulation may be harmful and associated with HT. In fact, previous studies showed that the presence of cerebral hyperperfusion in the MCA territory was associated with the development of hemorrhagic transformation after reperfusion therapy through neuroimaging studies using pulsed arterial spin labeling perfusion MRI, corroborating our TCCS results.[26,27] Furthermore, a TCSS study provided preliminary evidence that focal accelerations of blood flow velocities after MT may indicate a vessel wall injury induced by the application of stent retrievers.[28]

Several revascularization procedures such as carotid endarterectomy or stenting and basal cerebral arteries angioplasties can cause cerebral hyperperfusion syndrome (CHS) that increases the risk for HT and worsens the patients' prognosis.[29] The TCCS, due to its availability and practicability, is widely used in order to identify patients at risk for CHS through demonstration of postoperative hyperperfusion highlighting its potential usefulness in detection of hemodynamic changes in the cerebral circulation after revascularization therapies.[30]

The underlying mechanisms of ischemia-reperfusion injury in the brain are complex and dynamic, including oxidative stress, leucocytes infiltration, platelets activation and complement activation.[12,13] Among these mechanisms early blood-brain barrier (BBB) disruption is common and it has been associated to HT and poor clinical outcomes.[31] This early loss of BBB integrity

is characterized by an impaired cerebral autoregulation and acute elevation in regional cerebral blood flow within a few hours after reperfusion.[32] Hence, it is reasonable to speculate that early assessed hemodynamic changes on MCA perfusion by TCCS may be related with early BBB changes in the setting of reperfusion injury. Moreover, the important pathophysiological role played by BBB in ischemia-reperfusion injury mechanisms is enhanced when increased BBB permeability values assessed by perfusion CT were associated with HT after reperfusion therapies.[33,34] In addition, local vessel injury due to stent retrievers devices seems to be closely related to early BBB disruption.[35]

Thus, our data suggest that demonstration of MCA hyperperfusion after successful MT by early TCCS could be a feasible predictor of hemorrhagic transformation. It may make it possible to reduce potential complications of reperfusion injury in these high-risk patients through appropriate measures in useful time, such as blood pressure management, closely monitor for neurological deterioration and prevention of hematoma expansion.[36]

This study has several limitations that must be noted. Its retrospective nature decreases the accuracy and consistency of the measurement of variables. As a single-centered study, the results could reflect a local feature. The relative small number of patients included in our study do not allow a solid interpretation of our findings as well as the heterogeneous intervals in which TCCS were performed. Ultimately, the time from reperfusion to TCCS was not collected, not allowing a robust understanding of the TCCS data in the light of early BBB changes.

Conclusion

Early MCAsRo TCCS assessment in the first 24 hours is an independent predictor of HT in patients with anterior circulation LVO strokes after successful MT. These data suggest TCCS as a valid bedside screening method for the presymptomatic diagnosis of reperfusion injury.

Acknowledgments

Agradeço ao meu co-orientador, **Doutor João Sargento-Freitas**, por me ter concedido esta oportunidade de realizar investigação clínica no serviço de Neurologia-C e ter confiado em mim ao longo da concretização do trabalho. Algumas competências que fui adquirindo ao longo deste projeto deveram-se em grande parte à sua experiência nesta área e à sua acessibilidade para esclarecer todas as minhas dúvidas e preocupações.

À **Professora Doutora Isabel Santana**, minha orientadora, pela supervisão do rigor científico do presente trabalho.

Às **Doutoras Alexandra Silva e Joana Lopes e ao Doutor Jorge Lourenço** pela forma como me receberam no serviço de Neurologia-C, integrando-me na equipa e dando uma ajuda imprescindível nas fases iniciais do projeto.

À **Sara**, pela sua disponibilidade e rigor com que procedeu à revisão linguística do texto.

À minha **Família**, que incondicionalmente me tem apoiado ao longo do meu percurso académico, fazendo com que as adversidades sejam mais facilmente superadas.

Aos meus **Amigos e Colegas**, que me têm acompanhado ao longo destes 6 anos de vida académica e me têm proporcionado momentos que ficaram na minha memória.

Scientific Presentation

The present study has been submitted to the following congresses:

- 12º Congresso Português do AVC, 2018, Sociedade Portuguesa do Acidente Vascular Cerebral (SPAVC); (Oral Presentation Award)
- 23^{rd} Meeting of The European Society of Neurosonology and Cerebral Hemodynamics. (Poster Award)

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Supplemental Material

Supplemental Table I. Baseline Characteristics of the Study and Univariate Ordinal Regression for Predictors of 3-month mRS

Variable	Total Population, n=101 Patients	Univariate Association with 3-month mRS, β (95% CI)	*P* Value
Age, y, mean±SD	67.99±13.86	0.051 (0.025 to 0.078)	<0.001
Male gender, n (%)	59 (41.60)	0.150 (-0.544 to 0.844)	0.672
Smoking, n (%)	15 (14.90)	0.003 (-0.001 to 0.007)	0.108
Alcoholism, n (%)	11 (10.90)	0.003 (-0.001 to 0.007)	0.107
Hypertension, n (%)	60 (59.40)	0.003 (-0.001 to 0.007)	0.106
Diabetes mellitus, n (%)	19 (18.80)	0.003 (-0.001 to 0.007)	0.106
Dyslipidemia, n (%)	45 (44.60)	0.431 (-0.264 to 1.126)	0.224
Atrial fibrillation, n (%)	31 (30.70)	0.003 (-0.001 to 0.007)	0.107
Heart failure, n (%)	11 (10.90)	0.003 (-0.001 to 0.007)	0.107
Coronary artery disease, n (%)	11 (10.90)	0.003 (-0.001 to 0.007)	0.108
Previous mRS, mean±SD	0.36±0.74	0.294 (-0.182 to 0.771)	0.226
NIHSS at admission, mean±SD	16.42±6.25	0.062 (0.000 to 0.123)	0.049
Fibrinolysis (IV), n (%)	74 (73.30)	-0.317 (-1.091 to 0.458)	0.423
Time from symptom onset to thrombectomy, min, mean±SD	259.81±130.39	-0.001 (-0.004 to 0.002)	0.523

Dichotomous variables are presented as frequency (%). CI indicates confidence interval; SD, standard deviation; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; MFV, mean flow velocity; and MCA, middle cerebral artery.