Escola Superior de Tecnologia da Saúde
Politécnico de Coimbra

TRANSCRANIAL DOPPLER MONITORING OF BOTH MIDDLE AND POSTERIOR CEREBRAL ARTERIES CAN INCREASE MICROEMBOLIC SIGNALS DETECTION: A PILOT STUDY

Gilberto Agostinho Magalhães Pereira

Dissertação no âmbito do Mestrado em Fisiologia Clínica – Especialização em Ultrassonografia Cardíaca e Função Vascular, orientada pelo Professor Doutor Telmo Pereira e apresentada na Escola Superior de Tecnologias da Saúde de Coimbra para a obtenção do grau de Mestre em Fisiologia Clínica

Setembro de 2025

Escola Superior de Tecnologia da Saúde
Politécnico de Coimbra

TRANSCRANIAL DOPPLER MONITORING OF BOTH MIDDLE AND POSTERIOR CEREBRAL ARTERIES CAN INCREASE MICROEMBOLIC SIGNALS DETECTION: A PILOT STUDY

Gilberto Agostinho Magalhães Pereira

Dissertação no âmbito do Mestrado em Fisiologia Clínica – Especialização em Ultrassonografia Cardíaca e Função Vascular, orientada pelo Professor Doutor Telmo Pereira e apresentada na Escola Superior de Tecnologias da Saúde de Coimbra para a obtenção do grau de Mestre em Fisiologia Clínica

Setemebro de 2025

Ao Professor Pedro Castro, pela inestimável orientação, disponibilidade e contributo essencial para a concretização deste trabalho.

Ao Professor Telmo Pereira, pelo constante incentivo e controbuto fulcral para para a realização deste trabalho.

À minha família, por tudo o que representa, pelo amor, paciência e apoio incondicional em todas as fases desta jornada.

A lightning flash:

between the forest trees

I have seen water.

Masaoka Shiki

Trabalho de Projeto Original submetida à Escola Superior de Tecnologia da Saúde de Coimbra para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisiologia Clínica, realizado sob a orientação científica do Professor Doutor Telmo Pereira e coorientação do Professor Doutor Pedro Miguel Araújo Campos de Castro.

Constituição do Júri:

Presidente _____ [nome]

Vogal _____ [nome]

Vogal _____ [nome]

RESUMO

Introdução: Os acidentes vasculares cerebrais da circulação posterior representam 15–25% dos eventos isquémicos cerebrais e, embora menos frequentes do que os da circulação anterior, têm relevância clínica devido às dificuldades diagnósticas e ao risco limitação funcional e recorrência de eventos isquémicos. Os sinais microembólicos (MES) detetados por Doppler transcraniano (TCD) associam-se fortemente a aterosclerose de grandes vasos, mas podem ocorrer em várias etiologias. A monitorização de rotina de MES centra-se na avaliação das artérias cerebrais médias (ACM), negligenciando frequentemente as artérias cerebrais posteriores (ACP). O nosso objetivo foi avaliar se a inclusão da monitorização bilateral das ACP ao protocolo de rotina das ACM aumenta o número de MES detetados em doentes com AVC isquémico agudo, bem como analisar a sua relação com a etiologia do mesmo, bem como com a ecogenicicidade das estenoses ateroscleróticas carotídeas, com o grau de estenose arterial a montante, prognóstico funcional dos doentes aos 90 dias e a recorrência de eventos isquémicos até um ano.

Métodos: Estudo prospetivo, realizado num único centro, tendo sido incluídos doentes com AVC isquémico agudo de forma consecutiva e com qualquer etiologia, admitidos nas primeiras 48 horas após o início dos sintomas. Todos os doentes realizaram monitorização TCD de 30 minutos das artérias cerebrais média (ACM) e posterior (ACP) para deteção de MES. Os MES foram analisados quanto à sua presença e intensidade na análise espetral. Avaliou-se o outcome funcional dos doentes aos 90 dias (escala de Rankin modificada) e a recorrência de AVC, acidente isquémico transitório (AIT) ou embolismo sistémico até 360 dias. Os outcome foram comparados entre os grupos com e sem MES, com

análise adicional por etiologia do AVC e presença de estenose arterial no território a montante da artéria monitorizada. O estudo encontra-se registado em ClinicalTrials.gov (ID: 06735274).

Resultados: Entre 260 doentes, foram detetados MES em 17 (6,5%), com uma mediana de 3 eventos/hora (IQR 2–15). A deteção foi unilateral em 71% e ipsilateral ao hemisfério afetado em 76%. A monitorização da ACP permitiu identificar 4 casos adicionais positivos para MES (23,5% do total de positivos). Os doentes com MES apresentaram valores mais elevados de NIHSS (p = 0,047). A presença de MES na ACM associou-se a menor probabilidade de independência funcional aos 90 dias (OR ajustado 0,107, IC 95%: 0,022–0,526; p = 0,006). A taxa de recorrência foi de 8,1%, sendo mais elevada nos subgrupos com MES. A presença de MES associou-se a eventos isquémicos (log-rank p = 0,04; HR ajustado para ACP MES-positiva: 15,6, IC 95%: 1,5–157,8; p = 0,02). O número de MES foi mais elevado nos doentes com aterosclerose de grandes vasos (p < 0,01), enquanto a intensidade dos MES foi significativamente superior nos AVC cardioembólicos (p < 0,01). A presença e número de MES aumentaram com a gravidade da estenose, mas a intensidade dos mesmos foi inferior nos doentes com estenose carotídea ou vertebral a montante (p < 0,05).

Conclusão: Os nossos resultados demonstram que as características dos MES variam consoante a etiologia do AVC: a aterosclerose de grandes vasos associa-se a maior número de MES mas menor intensidade, enquanto os AVC cardioembólicos apresentam menos MES, mas de maior intensidade. A presença de MES associou-se a maior risco de recorrência quando detetada na ACP e a pior prognóstico funcional quando detetada na ACM. A monitorização

da ACP permitiu identificar casos adicionais de MES, reforçando o valor clínico de avaliar ambos os territórios na fase aguda do AVC.

PALAVRAS-CHAVE: sinais microembólicos, acidente vascular cerebral, ultrassonografia, Doppler transcraniano

ABSTRACT

Background: Posterior circulation strokes account for 15–25% of ischemic events and, although less frequent than anterior circulation strokes, they are clinically relevant due to diagnostic challenges and the persistent risk of disability and recurrence. Microembolic signals (MES) detected by transcranial Doppler (TCD) are strongly associated with large artery atherosclerosis but may occur across several etiologies. Routine MES monitoring focuses on the middle cerebral arteries (MCA), often neglecting the posterior cerebral arteries (PCA). Our objective was to evaluate whether the inclusion of bilateral PCA monitoring in addition to routine MCA monitoring increases the detection of MES in patients with acute ischemic stroke, as well as to analyze their relationship with stroke etiology, carotid plaque echogenicity, upstream arterial stenosis severity, functional outcome at 90 days, and recurrence of ischemic events up to one year.

Methods: This was a prospective single-center study of consecutive patients with acute ischemic stroke of any etiology, admitted within 48 hours of symptom onset. All patients underwent 30-minute TCD MES monitoring of both middle cerebral artery (MCA) and PCA arteries. MES were analyzed for both presence and intensity from the background signal. We evaluated functional outcome at 90 days using the modified Rankin Scale, and assessed for recurrence of stroke, TIA, or systemic embolism within 360 days. Outcomes were compared between MES-positive and MES-negative groups, with subgroup analysis based on stroke etiology and presence of arterial stenosis on the upstream territory. This study is registered at ClinicalTrials.gov (ID: 06735274).

Results: Among 260 patients, MES were detected in 17 (6.5%), with a median rate of 3 counts/hour (IQR 2–15). Detection was unilateral in 71% and ipsilateral

to the stroke side in 76%. PCA monitoring identified 4 additional MES-positive cases (23.5% of all positives). MES-positive patients had higher NIHSS scores ($p = 0.047$). MES in the MCA was associated with reduced odds of functional independence at 90 days (adjusted OR 0.107, 95% CI 0.022–0.526, $p = 0.006$). Recurrence occurred in 8.1% overall, with higher rates in MES-positive subgroups. MES presence predicted ischemic events (log-rank $p = 0.04$; adjusted HR for PCA MES-positive: 15.6, 95% CI 1.5–157.8, $p = 0.02$). MES burden was highest in large artery atherosclerosis ($p < 0.01$), while MES intensity was significantly greater in cardioembolic strokes ($p < 0.01$). MES presence and burden increased with stenosis severity, but MES intensity was lower in patients with upstream carotid and vertebral stenosis ($p < 0.05$).

Conclusion: Our findings show that MES characteristics differ by stroke etiology, with large artery atherosclerosis associated with higher burden and lower intensity, and cardioembolism with fewer but more intense signals; MES presence correlated with recurrence when detected in the PCA and poorer outcomes when detected in the MCA, while PCA monitoring revealed additional cases and showed embolic patterns comparable to those in the MCA, highlighting the value of assessing both circulations.

KEYWORDS

Microembolism, stroke, ultrasound, transcranial Doppler

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ACS: anterior circulation stroke

AF: atrial fibrillation

ASPECTS: Alberta Stroke Program Early Computed Tomography Score

BP: blood pressure

BNP: brain natriuretic peptide

CAD: coronary artery disease

CE: cardioembolic

CI: confidence intervals

CIM: cognitive impairment

CNS: central nervous system

CTA: computed tomography angiography

CT: computed tomography

DBP: diastolic blood pressure

ECST: European Carotid Surgery Trial

EBR: embolus-to-blood ratio

HR: Hazard ratio

HF: heart failure

HbA1c: hemoglobin A1c

hsTpI: high-sensitivity cardiac troponin

IQR: interquartile range

LAA: large artery atherosclerosis

LDL: low-density lipoprotein

MCA: middle cerebral artery

MES: microembolic signals

mRS: modified Rankin scale score

mTICI: modified Thrombolysis in Cerebral Infarction

MRI: magnetic resonance imaging

MRA: magnetic resonance angiography

NIHSS: National Institutes of Health Stroke Scale

OR: odds ratio

OSCP: Oxford Community Stroke Project classification

PAD: peripheral arterial disease

PCA: posterior cerebral artery

PCS: posterior circulation stroke

SBP: systolic blood pressure

SVO: small vessel occlusion

TCD: transcranial Doppler

TIA: transient ischemic attack

TOAST: Trial of Org 10172 in Acute Stroke Treatment

TABLE OF CONTENTS

Chapter I | INTRODUCTION

Posterior circulation strokes account for approximately 15–25% of all ischemic strokes and, despite being less common than anterior circulation events, they carry substantial clinical relevance owing to their heterogeneous presentations, frequent diagnostic delays, and non-negligible risk of disability even in minor strokes (Hendrix et al., 2022; Imam et al., 2024). While earlier studies suggested a higher early recurrence and disability risk at 3 months risk in PCS, more recent evidence confirms that patients with symptomatic vertebrobasilar stenosis remain at elevated risk, even with initially mild symptoms (Kim et al., 2017; Liu et al., 2023).

Microembolic signals (MES) detected by transcranial Doppler (TCD) have been described in patients with large artery atherosclerosis (King & Markus, 2009), dissection of large cervical vessels (Oliveira et al., 2001), atrial fibrillation and stroke (Castro et al., 2024), thrombectomy (Sheriff et al., 2020), carotid endarterectomy and stenting (Abbott et al., 2007) and atheromatous plaques in the aortic arch (Rundek et al., 1999), showing relationship with stroke recurrence and functional outcome. In terms of stroke etiology, large artery atherosclerosis continues to be one of the most strongly associated with MES (Bakola et al., 2025). Although comparable or even higher frequencies of MES have been reported in certain other determined etiologies, large vessel disease remains a consistent and well-established source of MES, in contrast to their relative rarity in small vessel disease. Standard MES detection by TCD protocols often dismisses the posterior cerebral artery (PCA) monitoring, or simply exclude PCS patients from the cohort, potentially overlooking embolic activity in this high-risk territory (Elsaid et al., 2020; Iguchi et al., 2007; Poppert et al., 2006). So, while most studies have focused on the the middle cerebral artery (MCA), the posterior circulation, supplied by the vertebrobasilar system, remains under-investigated (Hwang et al., 2012).

MES detection may aid in localizing embolic sources, stratifying risk, and guiding antiplatelet therapy, with evidence linking MES burden and intensity to plaque morphology and therapeutic response. Some data suggest that MES of low intensity, often dismissed as artifacts, may have prognostic value (Telman et al., 2011), and that plaque instability, rather than just stenosis degree, may be more predictive of embolic activity (Zhang et al., 2009).

We hypothesize that incorporating the PCA to the standard MCA only MES monitoring may not only improve detection rates but also help determine whether emboli in the posterior circulation exhibit similar or distinct characteristics, such as signal intensity and embolic burden, when compared to those in the anterior circulation. Furthermore, this approach could provide new insights into whether certain stroke etiologies have a greater tendency to affect the posterior circulation.

Our primary aim is to determine if the extended TCD monitoring to include more 30 minutes in both PCA in addition to routine MCA monitoring increases the number of MES detected in patients with acute ischemic stroke, as well as to analyze their relationship with stroke etiology, carotid plaque echogenicity, upstream arterial stenosis severity, functional outcome at 90 days, and recurrence of ischemic events up to one year.

Chapter II | METHODS

Study design, Patient selection and Ethics Considerations

We conducted a prospective single-center observational study involving consecutive ischemic stroke patients. We enrolled the patients admitted to the stroke unit at the Unidade Local de Saúde de São João in Porto, Portugal, between July of 2021 and November of 2022. Inclusion criteria for monitoring comprised a diagnosis of ischemic acute stroke, confirmed by neuroimaging (computed tomography - CT or magnetic resonance imaging - MRI) and able to be monitored within the first 48 hours. Eligible participants were required to be over 18 years of age, undergo transcranial TCD monitoring for a duration of 30 minutes for each artery (MCA and PCA), and have ethiological classification and stroke risk stratification performed using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, preferably within the first three months following study inclusion. For patients who underwent thrombectomy, we included those who achieved a grade of 2b-3 on the modified Thrombolysis in Cerebral Infarction Scale (mTICI). We excluded patients diagnosed with hemorrhagic stroke, non-vascular brain lesions (such as encephalitis and demyelinating disease), as well as those with mRS ≥4, previous cognitive impairment, active cancer, stroke mimics, renal disease, or intestinal disease. Additionally, patients without a temporal acoustic window for TCD examination were excluded, as well as any TCD recordings deemed of poor technical quality due to artifacts.

This study has been approved by the local institutional "Ethics Committee of Centro Hospitalar Universitário São João" (303/2020 - see Anexo) and been registered to ClinicalTrials.gov (Clinicaltrials.gov ID: 06735274). Written informed consents were obtained after a full description of the study to all participants/guardians.

Clinical, laboratory and radiological assessment

Demographic data and medical histories, including vascular risk factors, medication usage (specifically antithrombotic agents), and history of cardiovascular disease, were recorded. Blood pressure (BP), serum glucose, and cholesterol levels were measured upon admission. National Institutes of Health Stroke Scale (NIHSS) scores were obtained at baseline and reassessed 24 hours

after admission to the stroke unit. The classification of stroke type was conducted using the Trial of Org 10172 in TOAST scale.

Carotid stenosis was classified according to the European Carotid Surgery Trial (ECST) criteria, with four categories established: none, mild (<50%), moderate (50% to 69%), severe (≥70%), and occlusion ("Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST)", 1998). Lesions were further categorized based on echogenicity as uncomplicated or hypoechogenic and/or ulcerated. In cases where multiple imaging modalities were employed, computed tomography angiography (CTA) was prioritized over magnetic resonance angiography (MRA), and carotid ultrasound was utilized when no other modalities were available. Significant stenosis was defined as any degree of stenosis exceeding moderate levels (≥70%). Extracranial vertebral stenosis was primarily graded using CTA, with ultrasound being used in the absence of other imaging options (Hua et al., 2009; Lovrencić-Huzjan et al., 1999; Sidhu, 2000). Intracranial arterial stenosis was preferentially assessed by CTA, and transcranial color-coded duplex sonography was employed when no other imaging modalities were available (Baumgartner et al., 1999).

Microembolic signals detection

TCD monitoring was performed by a single trained investigator, within 72 hours of stroke unit admission. A single machine (Doppler Box X, DWL, Sipplingen, Germany) was used. The Doppler-BoxX system was operated using DWL's emboli detection software module (DWL Software, Doppler M-Mode with emboli module) to process MES signals. Bilateral M1 segments were insonated at a single depth (between 45mm and 55mm) for 30 minutes and after that a bilateral P2 segments insonation at a single depth (between 50mm and 70mm) for an additional 30 minutes, with 2-MHz transducers secured adjacently to the temporal bone window by a probe-fixation head frame (Marc 500, Spencer Technologies, Seattle, WA) with sample volume of 5 mm and low gain (Ringelstein et al., 1998). The presence and rate of MES were assessed by an experienced and certified

neurosonologist (GP) blinded to clinical data and outcomes and equiped with a head-set with noise cancelation in silent dedicated room.

An event was classified as MES based in international consensus criteria (Ringelstein et al., 1998). First, MES was identified by being an audible characteristic sounds (“snap” and/or “chirp”), with spectrogram visualization of unidirectional time course and short duration. In our study, we set 6 dB relative to the underlying flow signal (Ringelstein et al., 1998) (**Figure 1** displays an unilateral MES on M1 segment of the MCA and **Figure 2** displays an unilateral MES on P2 segment of the PCA). In doubtful cases the final decision was made with PC. Patients with one or more detected MES were classified into the three MES-positive subgroups (only MCA MES-positive, MCA and PCA MES-positive and only PCA MES-positive). The presence, burden and relative intensity of MES will be primary endopoits in this study.

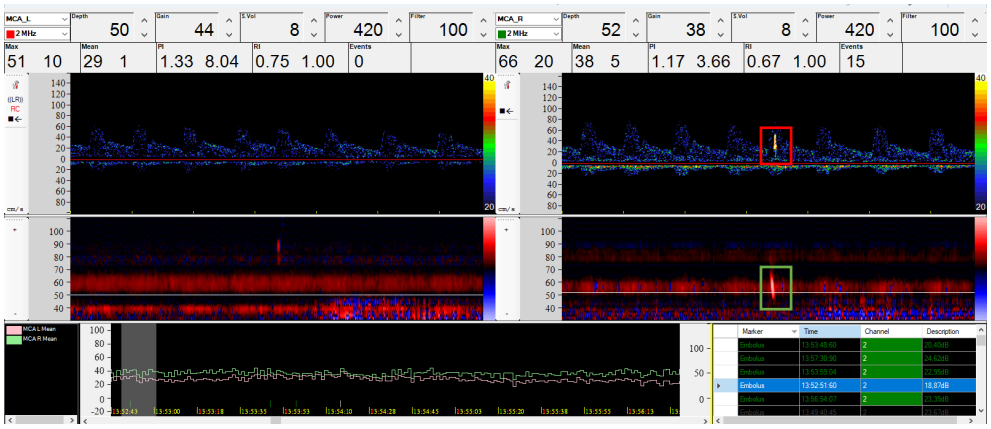

Figure 1: Microembolic signal on MCA TCD spectral wave (red square) and M mode (green square).

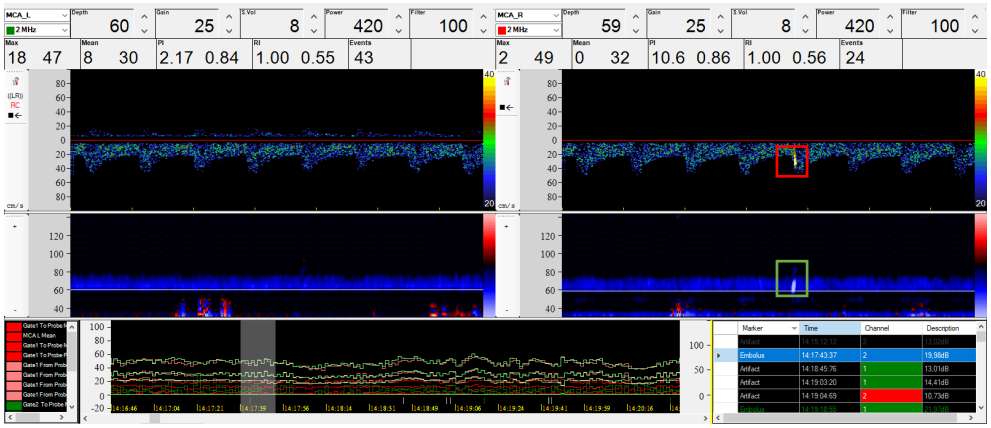

Figure 2: Microembolic signal on PCA TCD spectral wave (red square) and M mode (green square).

Clinical endpoints

The major endpoint was functional outcome at 90 days, measured by modified Rankin scale score (mRS). We compared the functional outcome across the whole scale (ordinal shift analysis) and by dichotomization of the mRS: 0-2 (independent) versus 3-6 (dependent or dead).

Finally, we compared ischemic stroke, TIA, or systemic embolism within 360 days. To detect these events, we interviewed patients and/or their caregivers and examined electronic medical records. Events were defined by clinical history, and all strokes were confirmed by head CT. Outcome ascertainment was blinded to the MES results.

Statistical Analysis

Normality of continuous variables was inferred by the Shapiro-Wilk test. The baseline characteristics of patients in the MES-positive and MES-negative groups were compared using chi-square/Fisher exact tests for categorical variables and Student's t/Mann-Whitney tests for continuous variables as appropriate. Bonferroni correction was used when categorical variables had more than one class. Clinical outcomes in the MES-positive subgroups and MES-negative groups were compared using mRS scores at 90 days with ordinal shift analysis modeling across all levels of the scale after verification of conformity to the assumption of a common proportional odds. Logistic regression was used to generate the odds ratios (OR) and 95% confidence intervals (CI) for functional independence (mRS 0 to 2 versus 3 to 6) at 360 days.

We adjusted analyses for all outcomes with one multivariate model. We adjusted to the independent variables associated with outcome in univariate analysis. This included age and NIHSS.

For the analysis of ischemic stroke/TIA recurrence or systemic embolism, the Kaplan-Meier method and log-rank Mantel-Cox test were used. Hazards ratios and 95% CI were estimated by Cox regression models. Due to the low number of these events, we only performed adjusted analysis by one covariate (propensity score).

All statistical analyses were performed with IBM SPSS Statistics for Windows, version 25. Statistical significance was inferred at $p<0.05$. Graphical representations were performed using GraphPad Prism, version 10 (GraphPad Software, San Diego, CA, USA).

Chapter III | RESULTS

Patient characteristics

From July 2021 to November 2022, 414 patients fulfilled the inclusion criteria. Of these, 154 patients were excluded due to absence of TCD recording of both MCA and PCA and/or insufficient temporal bone windows for TCD. Hence, we enrolled 260 patients (**Figure 3**).

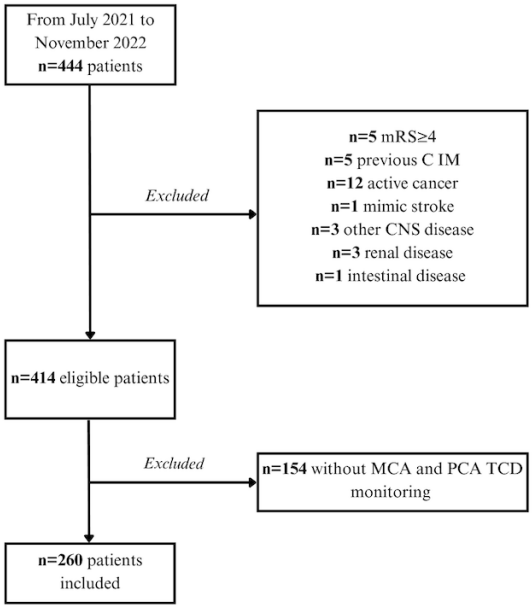

Figure 3: Flow chart of the study's recruitment.

Abbreviations: mRS: modified rankin scale; CIM: cognitive impairment; CNS: central nervous system; MCA: middle cerebral artery; PCA: posterior cerebral artery.

MES were detected on at least one side in 17 of 260 patients (6,5%). These patients constituted the MES-positive subgroups: MCA MES-positive (n=9), MCA and PCA MES-positive (n=4) and PCA MES-positive (n=4).

MES detection ranged from 1 to 45 counts with a median rate of 3/h (interquartile range [IQR] 2 – 15 counts/hour).

The groups showed significant differences in the distribution of MES-positive cases($p<0.001$]. Among the MES-positive cases, MCA alone accounted for 52,94% of detections (9 of 17), while PCA alone alone added 4 patients to the

MES-positive cases, corresponding to a global detection rate of 23,52% (4 of 17). 4 more patients had MES positive studies in both MCA and PCA 23,52% (4 of 17).

Table 1 presents a comparison of baseline characteristics between MES-positive subgroups and MES-negative group. Patients in the MES-positive subgroups demonstrated significantly higher NIHSS scores compared to the MES-negative group. Median (IQR) NIHSS scores were 10 (6–14) in the MCA MES-positive subgroup, 14 (10–14) in the MCA and PCA MES-positive subgroup, and 14 (11–17) in the PCA MES-positive subgroup, compared to 6 (3–11) in the MES-negative group (p=0.047).

A quarter of the patients in our cohort (n=68 patients; 26%) needed thrombectomy. These procedures were done on the anterior circulation in 64 patients (25%) and on the posterior circulation in 4 patients (2%). One of these patients had MES detected on the MCA (1 in 64 patients; 2%) and 2 had MES positive in PCA (2 in 4 patients; 50%).

MES-positive cases were independent across stroke etiologies, but most positive cases were on large vessel [6 (of the 17 MES positive patients, 35%)] and cardioembolic [5 (of the 17 MES positive patients, 29%)] group. Bilateral detection was infrequent n=5 and indistinct accordingly to etiology (p=0.567).

Table 1: Demographic, clinical and stroke characteristics and cardiac variables of all patients and the differences between MES-negative and all MES-positive (MCA MES-positive, both MCA and PCA MES-positive and PCA MES-positive) subgroups.

		MES negative	MES positive			
Variables	**Total (n=260)**	**None (n=243)**	**MCA+ (n=9)**	**MCA+PCA+ (n=4)**	**PCA+ (n=4)**	**P-value§**
Demographic and Clinical Variables						
Age [years; median (IQR)]	68 (60-76)	68 (59-76)	68 (58-72)	66.5 (55-71)	66 (62-71)	0.751
Female [n(%)]	94 (36)	84 (35)	6 (67)	2 (50)	2 (50)	0.207
BMI [kg/m²; median (IQR)]	27.0 (24.6-30.1)	27.0 (24.6-29.7)	30.5 (24.1-35.3)	25.0 (24.7-32.5)	29.0 (26.1-31.8)	0.560
Hypertension [n(%)]	181 (70)	170 (70)	5 (56)	3 (75)	3 (75)	0.810
Diabetes [n(%)]	74 (28)	66 (27)	5 (56)	2 (50)	1 (25)	0.223
Dyslipidemia [n(%)]	149 (57)	137 (56)	6 (67)	3 (75)	3 (75)	0.698
Smoker [n(%)]	47 (18)	44 (18)	1 (11)	1 (25)	1 (25)	0.907
Previous Stroke [n(%)]	35 (13)	31 (13)	2 (22)	1 (25)	1 (25)	0.657
Previous CAD [n(%)]	14 (5)	12 (5)	1 (11)	1 (25)	0 (0)	0.270
PAD [n(%)]	17 (7)	16 (7)	0 (0)	0 (0)	1 (25)	0.370
LDL [mg/dL; median (IQR)]	97.5 (71.5-128.0)	99 (73.0-128.0)	77 (70.0-88.0)	59.5 (54.0-109.0)	126.5 (94.0-163.5)	0.213
HbA1c [%; median (IQR)]	5.9 (5.5-6.5)	5.9 (5.5-6.4)	6.5 (5.7-8.4)	6.25 (6.0-7.0)	5.8 (5.5-6.1)	0.397
TOAST stroke classification						0.690
Large Vessel [n(%)]	50 (19)	44 (18)	2 (22)	2 (50)	2 (50)	
Cardioembolic [n(%)]	56 (22)	51 (21)	4 (44)	1 (25)	0 (0)	
Undetermined source [n(%)]	89 (34)	85 (35)	1 (11)	1 (25)	2 (50)	
Small Vessel [n(%)]	48 (18)	46 (19)	2 (22)	0 (0)	0 (0)	
High-dose statins at time of study [n(%)]	208 (80)	196 (81)	6 (67)	3 (75)	3 (75)	0.959
Anti-Coagulants at time of study [n(%)]	197 (76)	183 (75)	8 (89)	4 (100)	2 (50)	0.308
Dual Anti-Platelet Therapy [n(%)]	74 (28)	70 (29)	2 (22)	1 (25)	1 (25)	0.961

Continuation of Table 2: Demographic, clinical and stroke characteristics and cardiac variables of all patients and the differences between MES-negative and all MES-positive (MCA MES-positive, both MCA and PCA MES-positive and PCA MES-positive) subgroups.

Stroke Characteristics						
Onset-To-TCD-time [hours; median (IQR)]	39 (25-62)	39 (25-61)	59 (41-81)	26 (20-44)	29 (20-38)	0.170
NIHSS score [median (IQR)]	6 (3-12)	6 (3-11)	10 (6-14)	14 (10-14)	14 (11-17)	0.047*
Intravenous Thrombolysis [n(%)]	76 (29)	66 (27)	4 (44)	3 (75)	3 (75)	0.297
Thrombectomy [n(%)]	68 (26)	65 (27)	1 (11)	0 (0)	2 (50)	0.022*
Cardiac variables						
AF [n(%)]	54 (21)	49 (20)	4 (44)	1 (25)	0 (0)	0.239
SBP [mmHg; median (IQR)]	136 (122-151)	136 (122-150)	126 (120-161)	131 (116-144)	147 (130-178)	0.634
DBP [mmHg; median (IQR)]	74 (65-83)	74 (66-83)	78 (66-90)	61 (58-74)	73 (61-84)	0.464
hsTpI [ng/L; median (IQR)]	10.8 (4.3-18.0)	9.7 (4.2-18.0)	18.2 (13.4-28.7)	14.1 (6.7-29.2)	31.1 (3.9-2183.5)	0.126
BNP [pg/mL; median (IQR)]	77.4 (28.7-225.7)	74.05 (28.3-225.7)	162.8 (68.3-285.1)	51.7 (17.2-84.3)	165.8 (110.3-2001.0)	0.189
HF [n(%)]	15 (6)	14 (6)	1 (11)	0 (0)	0 (0)	0.810

Abbreviations: MES: microembolic signals; MCA: middle cerebral artery; PCA: posterior cerebral artery; CAD: corornary artery disease; PAD: periferal arterial disease; LDL: low density lipoprotein; IQR: interquartile range; HbA1c: hemoglobin A1c; TOAST: Trial of Org 10172 in Acute Stroke Treatment; TCD: transcranial Doppler; NHISS: Scores on the National Institutes of Health Stroke Scale; AF: atrial fibrilation; SBP: systolic blood pressure; DBP: diastolic blood pressure; hsTpI: high sensitivity cardiac troponin; BNP: Brain natriuretic peptide; HF: heart failure

§ P-values indicate differences between MES-positive subgroups and the MES-negative group, assessed using chi-square or Fisher's exact tests for categorical variables and Student's t-test or Mann–Whitney test for continuous variables. * For multiple comparisons, the Bonferroni correction was applied, with the significance threshold adjusted to $P < 0.05$ divided by the number of comparisons.

Table 2 shows the results from the comparison of outcomes between the MES-negative and MES-positive subgroups. The presence of MES on the MCA was strongly associated with reduced odds of achieving independence at 90 days. Patients with MCA MES-positive had an odds ratio of 0.107 (95% CI: 0.022–0.526; p = 0.006), indicating that the odds of achieving independence were approximately 89.3% lower compared to patients without MES. There was no difference in functional outcomes between the other MES-positive subgroups and the MES-negative group.

Table 3: Outcome measures based on MES-negative and all MES-positive (MCA MES-positive, both MCA and PCA MES-positive and PCA MES-positive) subgroups.

Abbreviations: CI: confidence interval; MES: microembolic signals; MCA: middle cerebral artery; PCA: posterior cerebral artery; mRS: modified Rankin Scale.

*Multivariate model 1 = adjusted to predictors of outcome – age, NIHSS, Last-seen-well to canalization time (hours), the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), modified Thrombolysis in Cerebral Infarction (mTICI).

‡Univariate and multivariate analysis with ordinal shift analysis to predict outcome

Outcome Measures	MES subgroups	Univariate Model - Unadjusted Odds Ratio (CI 95%); P-value	Multivariate Model - Adjusted Odds Ratio (CI 95%); P- value
mRS 0–2 at 90 days – n (%)	MES-negative (n=243) vs MCA MES-positive (n=9)	0.107 [0.022–0.526]; p=0.006	0.091 [0.017–0.482]; p=0.005
	MES-negative (n=243) vs MCA and PCA MES-positive (n=4)	0.124 [0.013–1.216]; p=0.073	0.126 [0.010–1.638]; p=0.113
	MES-negative (n=243) vs PCA MES-positive (n=4)	0.373 [0.051–2.701]; p=0.329	0.514 [0.006–4.033]; p=0.527

Stroke or systemic embolism recurrence

There was a total of 17 recurrent ischemic events, representing an event in 6,50% of the entire cohort. The PCA MES-positive subgroup exhibited the highest recurrence rate compared to other MES-positive subgroups and the MES-negative group. Specifically, the recurrence rates were 25% (1/4) in the PCA MES-positive subgroup, 25% (1/4) in the MCA and PCA MES-positive subgroup, and 22.22% (2/9) in the MCA MES-positive subgroup, while the MES-negative group had a recurrence rate of 7,02% (17 events out of 242 patients).

Time-dependent change in risk showed significantly higher risk of embolic events (**Figure 4**, log rank test p=0.04) in all the MES-positive subgroups.

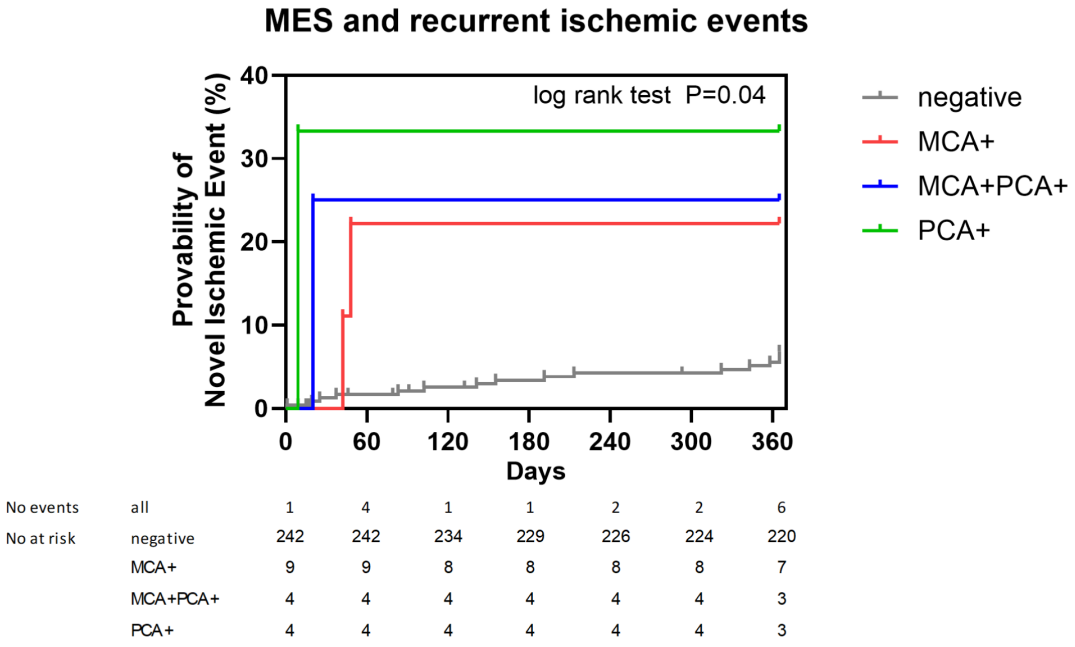

Figure 4: Kaplan-Meier survival curves for event recurrence within 360 days from index stroke.
Abbreviations: MES: microembolic signals; MCA: middle cerebral artery; PCA: posterior cerebral artery.

Eleven patients died during study follow-up (4,3%); all of them in the MES-negative group. There was no correlation between the presence of MES and all-

cause mortality in either the Kaplan-Meier survival analysis (log-rank test p = 0.858) nor the Cox-regression hazard model.

Cox-regression hazard model (**Table 3**) showed that PCA MES-positive patients had higher risk of having an ischemic stroke/TIA at follow-up compared to the MES-negative patients (unadjusted HR 7,717 CI 95% 1,014-58,738; p=0.048)

Table 4: Comparison of the risk of ischemic stroke/TIA and composite outcome vascular event in patients with MES-negative and all MES-positive (only MCA MES-positive, both MCA and PCA MES-positive and only PCA MES-positive) subgroups, using Cox proportional hazard regression.

	Recurrent ischemic stroke or TIA			***Composite Outcome**		
	Unadjusted analysis					
	n	HR [95% CI]	p-value	n	HR [95% CI]	p-value
MCA MES-positive (n=9)	2	4,161 (0,945-18,333)	0,059	2	3,463 (0,800-14,995)	0,097
MCA and PCA MES-positive (n=4)	1	5,057 (0,664-38,481)	0,118	1	4,175 (0,555-31,384)	0,165
PCA MES-positive (n=4)	1	7,717 (1,014-58,738)	0,048	1	6,311 (0,839-47,464)	0,073
MES-negative (n=243)	14	Reference		17	Reference	

Abbreviations: CI = confidence interval; HR = Hazard Ratio; MES = Microembolic Signals; TIA = transient ischemic attack; MCA: middle cerebral artery; PCA: posterior cerebral artery; * Composite outcome: ischemic stroke, TIA, systemic embolism;

MES presence, burden, intensity and association with stroke etiology

Stroke etiology was not significantly different across MES-positive subgroups (p-value: 0,690). In the MCA only MES-positive subgroup, 44% of MES-positive patients were associated to cardioembolic source, while 22% were attributed to large vessel atherosclerosis. Both in MCA and PCA MES-positive and PCA only MES-positive subgroups, the majority of MES were associated to large vessel atherosclerosis (50% in both subgroups).

As seen on **Figure 5**, MES burden (counts) was highest in the LAA stroke patients across all MES-positive subgroups compared to SVO stroke patients ($p<0.01$). For SVO stroke patients, MES burden was significantly lower across all territories, serving as the reference group for stroke type. The CE subgroup demonstrated intermediate MES burden rate, with no significant difference compared to the other groups ($p>0.05$).

Figure 6 demonstrates that MES intensity (intensity, dB; IQR) was significantly higher in CE for MCA (18, 10-21) and for PCA (15, 9-19) (p-value < 0,01). In LAA strokes, MES intensity remained lower in both arterial territories (for MCA: 11, 7-17 and for PCA: 10, 7-16; p-value<0,05).

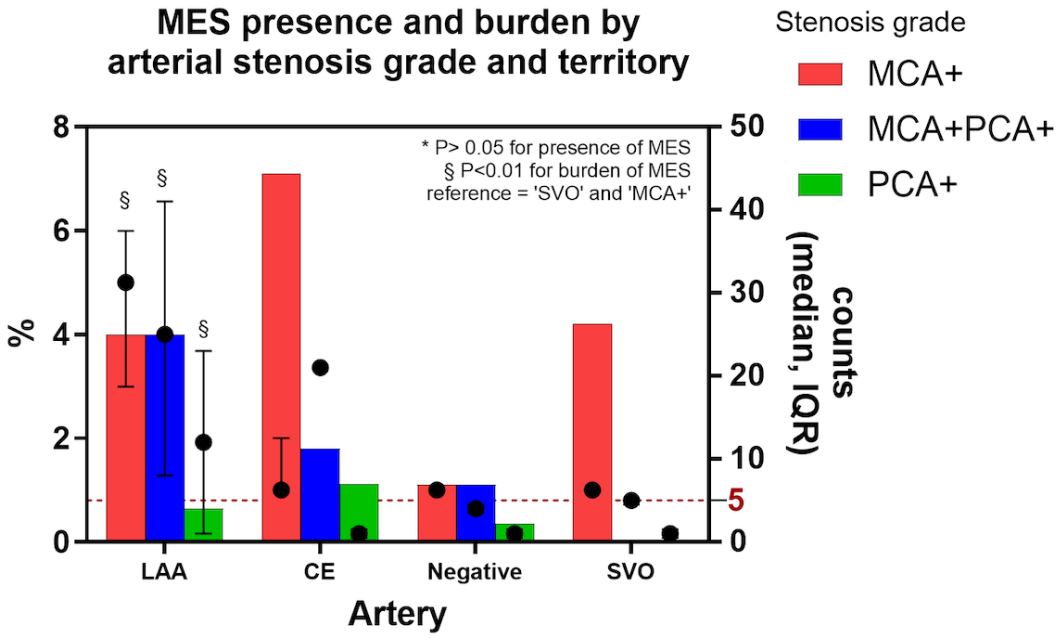

Figure 5: Presence and burden of MES across different stroke etiologies (LAA, CE, Negative, and SVO) and MES-positive subgroups arterial (MCA+, MCA+PCA+, and PCA+). The y-axis on the left represents the percentage of patients with MES, while the y-axis on the right displays the MES burden as median counts and interquartile range (IQR).

(continuation from Figure 5) Abbreviations: MES: microembolic signals; MCA: middle cerebral artery; PCA: posterior cerebral artery; LAA: large artery atherosclerosis; CE: cardioembolic; SVO: small vessel occlusion.

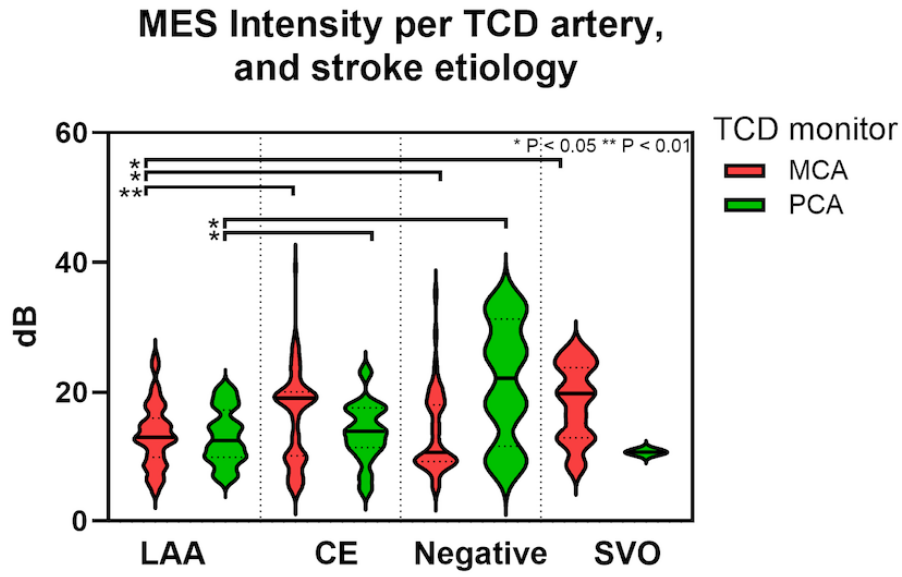

Figure 6: Distribution of MES intensity (measured in dB) across different stroke etiologies (LAA, CE, Negative, SVO) and arterial territories (MCA in red and PCA in green).
Abbreviations: MES: microembolic signals; TCD: transcranial doppler; MCA: middle cerebral artery; PCA: posterior cerebral artery; LAA: large artery atherosclerosis; CE: cardioembolic; SVO: small vessel occlusion.

MES presence, burden, and intensity in relation to ipsilateral carotid plaque echogenicity

The presence and burden of MES were strongly associated with carotid atherosclerotic plaque caracheristics (**Figure 7**). Hypoechoic/ulcerated carotid atherosclerotic plaques demonstrated the highest MES burden, with a median MES count of 10 (8–12), significantly exceeding both hyperechoic plaques (4, 3–6) and cases without detectable atherosclerotic plaques (2, 1–3). MES presence was also significantly higher in the hypoechoic/ulcerated group ($p<0.05$) compared to the reference group (no carotid atherosclerotic plaques).

The intensity of MES did not differ significantly among the three groups ($p>0.05$; **Figure 8**). The median MES intensity was higher in patients with hyperechoic carotid plaques (19, 13–20), but showed no statistically significant differences

when compared to hypoechoic/ulcerated plaques (13, 9-18) and patients with no carotid plaques (10, 9–14).

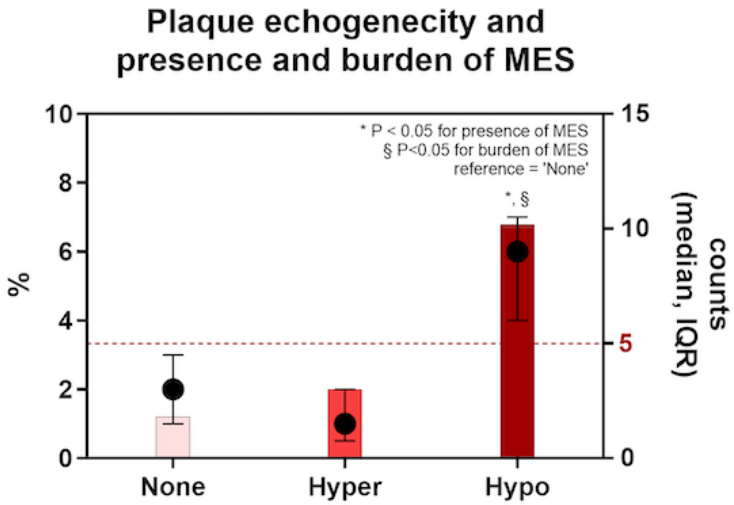

Figure 7: Distribution of MES counts (presence and burden) on ipsilateral MCA according to carotid atherosclerotic plaque echogenicity (hyperecoic and hypoecoic) and the absence of plaque (reference).
Abbreviations: MES: microembolic signals; IQR: interquartile range; Hyper: hyperecoic atherosclerotic plaque; Hypo: hypoecoic atherosclerotic plaque.

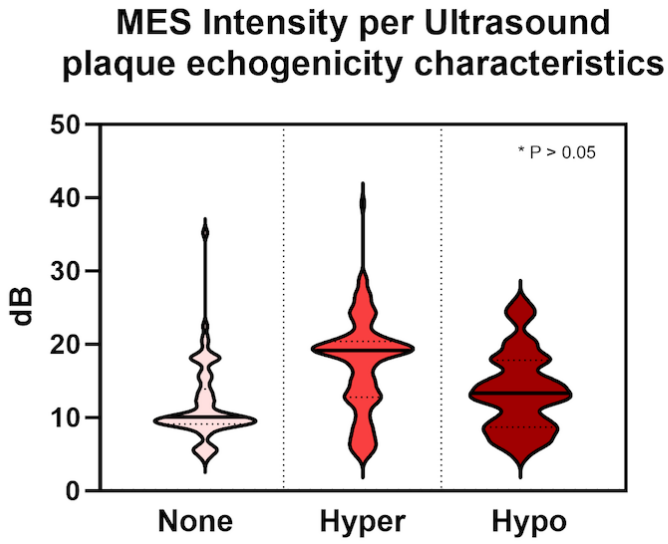

Figure 8: Distribution of MES intensity on ipsilateral MCA according to carotid atherosclerotic plaque echogenicity (hyperecogenic and hypoecogenic) and the absence of plaque (reference).
Abbreviations: MES: microembolic signals; IQR: interquartile range; Hyper: hyperecoic atherosclerotic plaque; Hypo: hypoecoic atherosclerotic plaque.

MES Presence, Burden and Intensity by Arterial Stenosis Grade and Arterial Territory

Figure 9 show that MES presence and burden increased with the severity of carotid stenosis, peaking in severe stenosis (p-value<0,05 for MES burden), when compared to carotid stenosis free patients. Vertebral artery also demonstrated the higher MES presence and burden (p-value<0,05 for MES presence and burden) in severe stenosis when compared with vertebral stenosis free patients.

Data on **Figure 10** shows that MES intensity between stenosis grades stenosis is lower compared to the "no stenosis" group. Particularly in the carotid territory, there is a statistically significant difference ("∗" for p-value<0.05) between the MES intensity measured in patients stenosis compared to the stenosis free group. We also see that tendency in the vertebral territory where MES intensity in patients with severe stenosis in the upstream territory show lower values compared to the stenosis free group (p-value<0,05). Even though MCA show similar data, there is no significant differences between the severe stenosis and stenosis free groups (p-value>0,05).

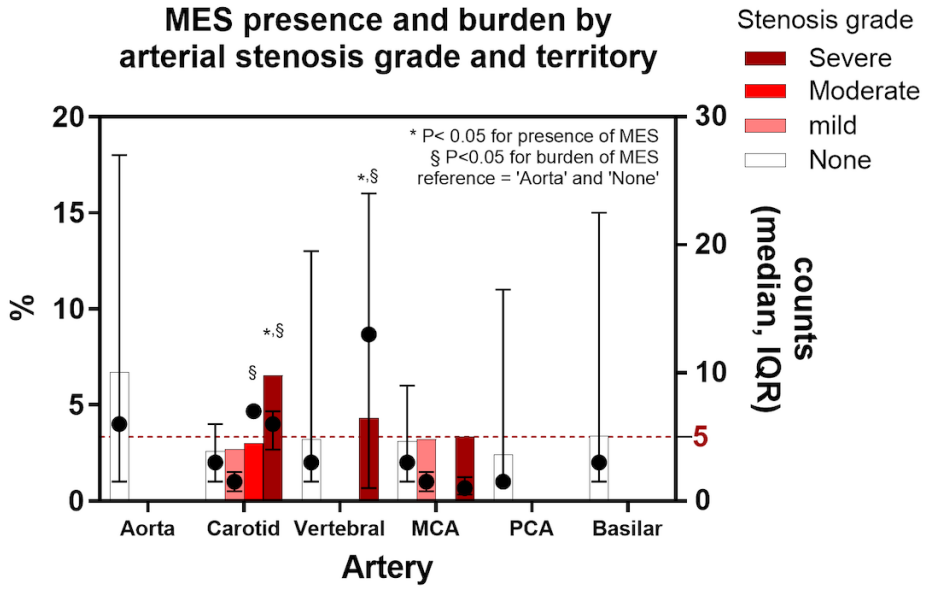

Figure 9: MES presence and burden stratified arterial stenosis grade (None, Mild (0-49%), Moderate (50-70%), and Severe (>70%)) in the upstream arterial territories (Aorta, Carotid, Vertebral, MCA, PCA, and Basilar). The left y-axis represents the percentage of patients with MES presence in both MCA (for Aorta), in the ipsilateral MCA (for carotid and MCA stenosis), in both PCA (for vertebral and basilar stenosis), in ipsilateral PCA for (PCA stenosis and carotid stenosis with fetal ipsilateral posterior cerebral artery), while the right y-axis reflects MES burden as median counts and IQR. This analysis was performed exclusively on patients with both MCA and PCA monitoring, resulting in some arteries (e.g., Aorta, Basilar and PCA) having incomplete data. "*"marked significant differences (p-value < 0.05) for presence of MES; "§" marked significant differences (p-value < 0.05) for burden of MES; for reference were used "Aorta" and "None".
Abbreviations: MES: microembolic signals; IQR: interquartile range; MCA: middle cerebral artery; PCA: posterior cerebral artery.

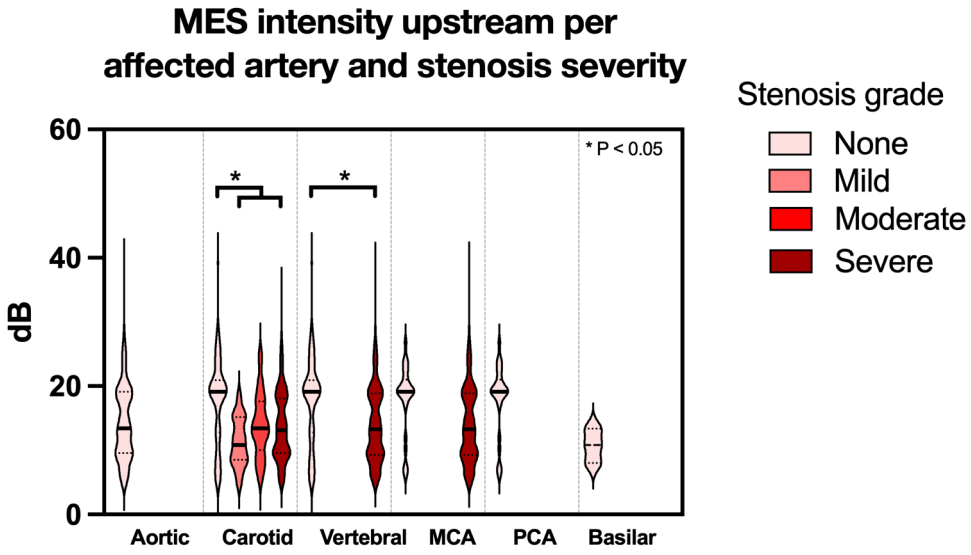

Figure 10: MES intensity stratified arterial stenosis grade (None, Mild (0-49%), Moderate (50-70%), and Severe (>70%)) in the upstream arterial territories (Aorta, Carotid, Vertebral, MCA, PCA, and Basilar). The y-axis represents the MES intensity in decibels (dB). The violin plots represent the distribution of MES

(continuation from Figure 10) intensity, with the median and interquartile ranges overlaid. Significant differences ("*" for $p<0.05$) are marked between groups. This analysis was performed exclusively on patients with both MCA and PCA monitoring, resulting in some arteries (e.g., Aorta, Basilar and PCA) having incomplete data.

Abbreviations: MES: microembolic signals; TCD: transcranial doppler ultrasound; MCA: middle cerebral artery; PCA: posterior cerebral artery.

Chapter IV | DISCUSSION

In this prospective observational study of patients with acute ischemic stroke, MES detection by TCD identified MES in 6,5% of cases. Previous studies showed a large variability of positive MES rates between 17 and 40% (Castro et al., 2024; Ritter et al., 2008; Sheriff et al., 2020). We included strokes of various etiologies and an extended monitoring period during the acute phase. The median time between the last known well time and TCD monitoring was higher than in previous studies, which may explain the lower prevalence of MES positive patients. Previous studies show that MES are more frequent in the first hours following an ischemic stroke and gradually decrease in the days after the event. A recent study with repeated TCD monitoring over time demonstrated that patients who tend to be MES-negative within the first 24 hours are likely to remain so (Aarli et al., 2024).

The presence of MES has also been described as a common occurrence following endovascular treatments in the acute phase. In our results, thrombectomy was related with a higher percentage of patients with MES positive studies, particularly in the PCA. The association wasn't stronger perhaps because thrombectomy was needed in only 26% of our patients, compared to other cohorts that focused on MES detection after thrombectomy that showed 39% MES detection rate (Sheriff et al., 2020).

Patients in the MES positive subgroups tended to have higher NIHSS scores, particularly the MCA+PCA+ subgroup and the PCA+ subgroup when compared to the MES negative subgroup. The PCA supplies blood to critical brain regions such as the brainstem and cerebellum. The presence of MES in this artery may indicate embolization originating from upstream arterial sources and even from the anterior circulation (in cases of a fetal-type posterior cerebral artery),

suggesting a potentially more complex and severe stroke etiology. Furthermore, the PCA has a more limited collateral network, which may compromise hemodynamic compensation in the event of vessel stenosis or occlusion (Lee et al., 2022).

Although not statistically significant, MES tended to occur more frequently in patients with diabetes, dyslipidemia, prior coronary or peripheral artery disease, and higher LDL and HbA1c levels. These factors are associated with unstable atherosclerotic plaques, which may serve as sources of cerebral emboli. This trend highlights the potential value of posterior circulation MES monitoring in patients with multiple vascular risk factors to better assess stroke severity and guide targeted interventions (Bazan et al., 2020). Several studies suggest that elevated BNP and hs-cTnT levels in MES-positive patients may reflect subclinical cardiac dysfunction and ongoing embolic risk, providing a mechanistic link between cardiac health and embolic activity (Faiz et al., 2014; Pokharel et al., 2019). Monitoring these biomarkers alongside TCD detection of MES could improve risk stratification, guide targeted interventions, and help identify patients at higher risk of severe neurological impairment.

MES burden, recurrence, and functional outcome

We recorded 21 recurrent ischemic events, representing an event in 8,14% of the entire cohort. MES-positive subgroup only accounted for a total of 4 recurrent events (stroke, TIA or other embolic event). This low incidence of recurrent events is inevitably related to aggressive therapy in the acute phase, with stenting and endarterectomy in high grade arterial stenosis and the implementation of dual antiplatelet therapy in high-risk patients. Even though most of recurrent events

happened in the MES negative group (n=17), time-dependent change in risk showed significantly higher risk of embolic events, and particularly ischemic stroke/TIA in all the MES-positive subgroup. Given the low number of recurrent events, further modeling with Cox-regression hazard model was not factored in, as it may lead to overfitting and unreliable estimates.

The presence of MES was associated with a increased risk of ischemic stroke/TIA or systemic embolization, suggesting that MES may be considered an independent risk factor for recurrent vascular events. This finding is in accordance with various studies which have demonstrated that MES predict increased risk of future cerebral ischemia after an acute stroke (Das et al., 2020; Gao et al., 2004; Ritter et al., 2008). Most of these studies address the predictive value of MES in carotid stenosis. In our study, all patients with high-grade carotid stenosis were symptomatic and were treated with endarterectomy/stenting. This would be expected to lower the stroke recurrence and may have underestimated the stroke recurrence rate in our cohort.

In our cohort, MCA MES-positive patients had markedly reduced odds of achieving independence at 90 days, with approximately 89.3% lower odds compared to MES-negative patients. No significant differences in functional outcomes were observed for other MES-positive subgroups. These findings align with previous studies reporting worse functional outcomes in patients with MCA-detected MES (Castro et al., 2024; Das et al., 2020). However, they contrast with studies focusing exclusively on post-thrombectomy patients, typically those with more severe strokes, where MES presence did not consistently predict functional outcomes (Sheriff et al., 2020). This suggests that the impact of MES on prognosis may be influenced by stroke severity and treatment context,

highlighting the particular clinical relevance of TCD embolic activity assessment in predicting post-stroke status

.

MES burden and intensity and stroke etiology

Our study found that MES burden was highest in patients with large artery atherosclerosis stroke and lowest in small vessel occlusion stroke patients (Figure 4), while MES intensity was significantly greater in cardioembolic stroke (Figure 5). This behavior was reported before in patients with acute ischemic stroke with multiple different etiologies that had done MCA MES detection (Bakola et al., 2025; King & Markus, 2009). Notably, we found that in LAA patients, MES intensity remained consistently lower across all stroke etiologies, in both MCA and PCA. In Figure 6 we also can see that hypoecoic atherosclerotic plaques have a higher rate of presence and burden of MES when compared to patients with hyperecoic plaques, with no significantly different MES intensity across the different types of plaques (as seen in Figure 7). These findings suggest that not only the quantity but also the qualitative characteristics of microemboli differ by stroke mechanism, with apparently similar behavior in both anterior and posterior circulation. This observation aligns with existing histopathological studies that describe distinct differences in the composition and structure of emboli based on their origin (Roessler et al., 2021). Arteriosclerotic emboli are primarily composed of agglutinative thrombi with fine fibrin networks, high concentrations of red blood cells and intact neutrophils, and few platelets. The disturbed flow patterns and shear forces associated with high-grade stenoses can promote platelet activation and fibrin deposition downstream, leading to the formation of unstable, red cell-rich agglutinative thrombi. Such

physical properties likely contribute to their fragmentation potential, resulting in a higher number of smaller, lower-intensity MES detected on TCD. In contrast, cardioembolic thrombi are characterized by dense fibrin networks, numerous platelets, and lower proportions of intact red blood cells and granulocytes. These emboli tend to be compact, rigid, and more structurally mature, which may translate into fewer but more intense signal on TCD.

It has been suggested that when thrombus fragments are smaller than 0.3 mm in diameter, the correlation between microemboli-to-bolus ratio (MEBR) and thrombus size tends to approach zero (Chung et al., 2006). So, in the context of large artery atherosclerosis, although MES burden appears higher in these patients, the actual extent of embolic activity may be underestimated by transcranial Doppler (TCD). The small size and friable nature of arteriosclerotic emboli likely contribute to limited signal detectability, potentially leading to an underrepresentation of the true embolic load.

Our findings demonstrate a clear association between the severity of extracranial stenosis and increased MES detection. In the anterior circulation, we observed that both the presence and burden of MES in the MCA increased with the degree of carotid stenosis, reaching statistical significance for MES presence and burden in cases of severe stenosis (Figure 8). A comparable pattern was evident in the posterior circulation, where severe vertebral artery stenosis was significantly associated with higher rates of MES detection in the PCA (Figure 8). Notably, despite the elevated embolic burden in patients with upstream stenosis, the MES intensity recorded in both MCA and PCA territories was lower than in patients without significant stenosis in the upstream of the corresponding arteries. This supports the notion referred earlier that microemboli originating from LAA are

typically of lower intensity, likely reflecting their distinct histological composition compared to emboli from other stroke etiologies.

Chapter V | LIMITATIONS

To assess both the MCA and PCA, each artery was monitored separately for 30 minutes, regardless of the lesion's location. While this approach allowed for comprehensive territorial evaluation, it is shorter than the recommended minimum of one hour, which has been shown to improve the sensitivity of microemboli detection and provide a more reliable assessment of embolic burden (Aarli et al., 2024; Ringelstein et al., 1998). This shorter monitoring duration was chosen as a practical compromise to facilitate the integration of the study into the routine workflow of the stroke unit without interfering with standard patient care.

Differences in baseline characteristics between MES groups may have introduced bias. Patients in the MES-positive group had higher NIHSS scores and were more frequently referred for endovascular treatment, interventions known to cause vascular or endothelial injury, which may, in turn, increase MES detection independently of stroke etiology. However, as our cohort represents a convenience sample drawn from routine clinical practice, it may realistically reflect the patient population typically encountered in a stroke unit, thereby offering insights that are both clinically relevant and generalizable.

The relatively small number of recurrent events may have limited the statistical power of our risk estimates, increasing the possibility of a type II error. Additionally, the absence of MRI in our protocol may have limited our ability to detect clinically silent ischemic lesions that could correspond to ischemic events.

Chapter VII | CONCLUSIONS

In conclusion, our exploratory findings suggest that MES characteristics may vary according to stroke mechanism, with large artery atherosclerosis tending to produce a higher burden of lower-intensity signals, and cardioembolic strokes appearing to be associated with fewer but more intense MES, possibly reflecting differences in thrombus composition. The presence of MES in the PCA was observed alongside a trend toward increased risk of recurrent ischemic events, while MES in the MCA appeared to be linked with poorer functional outcomes. Importantly, including PCA monitoring allowed detection of additional MES-positive cases, highlighting the potential value of assessing both anterior and posterior circulations to capture embolic activity more comprehensively. Notably, MES detected in the PCA exhibited patterns of burden and intensity broadly similar to those seen in the MCA, suggesting that embolic behavior may be comparable across these vascular territories. These findings are preliminary, warranting further investigation in larger, confirmatory studies.

Chapter VII | REFERENCES

Aarli, S. J., Thomassen, L., Logallo, N., Kvistad, C. E., Næss, H., & Fromm, A. (2024). Prolonged and repeated microemboli detection in acute ischemic stroke - The Norwegian Microemboli in Acute Stroke Study (NOR-MASS). *J Stroke Cerebrovasc Dis*, *33*(9), 107849. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107849

Abbott, A. L., Levi, C. R., Stork, J. L., Donnan, G. A., & Chambers, B. R. (2007). Timing of clinically significant microembolism after carotid endarterectomy. *Cerebrovasc Dis*, *23*(5-6), 362-367. https://doi.org/10.1159/000099135

Bakola, E., Palaiodimou, L., Kargiotis, O., Safouris, A., Psychogios, K., Karapanayiotides, T.,…Georgios, T. (2025). Microembolic signal detection in acute ischemic stroke: Clinical relevance and impact on treatment individualization-A narrative review. *Eur J Neurol*, *32*(1), e16584. https://doi.org/10.1111/ene.16584

Baumgartner, R. W., Mattle, H. P., & Schroth, G. (1999). Assessment of >/=50% and <50% intracranial stenoses by transcranial color-coded duplex sonography. *Stroke*, *30*(1), 87-92. https://doi.org/10.1161/01.str.30.1.87

Bazan, R., Luvizutto, G. J., Braga, G. P., Bazan, S. G. Z., Hueb, J. C., de Freitas, C. C. M.,…Pontes-Neto, O. M. (2020). Relationship of spontaneous microembolic signals to risk stratification, recurrence, severity, and mortality of ischemic stroke: a prospective study. *Ultrasound J*, *12*(1), 6. https://doi.org/10.1186/s13089-020-0156-1

Castro, P., Ferreira, J., Malojcic, B., Bazadona, D., Baracchini, C., Pieroni, A.,…Kaps, M. (2024). Detection of microemboli in patients with acute ischaemic stroke and atrial fibrillation suggests poor functional outcome. *Eur Stroke J*, *9*(2), 409-417. https://doi.org/10.1177/23969873231220508

Chung, E. M., Fan, L., Naylor, A. R., & Evans, D. H. (2006). Characteristics of Doppler embolic signals observed following carotid endarterectomy. *Ultrasound Med Biol*, *32*(7), 1011-1023. https://doi.org/10.1016/j.ultrasmedbio.2006.03.007

Das, A. S., Regenhardt, R. W., LaRose, S., Monk, A. D., Castro, P. M., Sheriff, F. G.,…Vaitkevicius, H. (2020). Microembolic Signals Detected by Transcranial

Doppler Predict Future Stroke and Poor Outcomes. *J Neuroimaging*, *30*(6), 882-889. https://doi.org/10.1111/jon.12749

Elsaid, N., Bigliardi, G., Dell'Acqua, M. L., Vandelli, L., Ciolli, L., Picchetto, L.,…Saied, A. (2020). The Relation Between Aortic Arch Branching Types and the Laterality of Cardio-Embolic Stroke. *J Stroke Cerebrovasc Dis*, *29*(7), 104917. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104917

Faiz, K. W., Thommessen, B., Einvik, G., Brekke, P. H., Omland, T., & Rønning, O. M. (2014). Determinants of high sensitivity cardiac troponin T elevation in acute ischemic stroke. *BMC Neurol*, *14*, 96. https://doi.org/10.1186/1471-2377-14-96

Gao, S., Wong, K. S., Hansberg, T., Lam, W. W., Droste, D. W., & Ringelstein, E. B. (2004). Microembolic signal predicts recurrent cerebral ischemic events in acute stroke patients with middle cerebral artery stenosis. *Stroke*, *35*(12), 2832-2836. https://doi.org/10.1161/01.STR.0000147035.31297.b6

Hendrix, P., Killer-Oberpfalzer, M., Broussalis, E., Melamed, I., Sharma, V., Mutzenbach, S.,…Griessenauer, C. J. (2022). Mechanical Thrombectomy for Anterior versus Posterior Circulation Large Vessel Occlusion Stroke with Emphasis on Posterior Circulation Outcomes. *World Neurosurg*, *158*, e416-e422. https://doi.org/10.1016/j.wneu.2021.10.187

Hua, Y., Meng, X. F., Jia, L. Y., Ling, C., Miao, Z. R., Ling, F., & Liu, J. B. (2009). Color Doppler imaging evaluation of proximal vertebral artery stenosis. *AJR Am J Roentgenol*, *193*(5), 1434-1438. https://doi.org/10.2214/ajr.09.2624

Hwang, J., Kim, S. J., Hong, J. M., Bang, O. Y., Chung, C. S., Lee, K. H., & Kim, G. M. (2012). Microembolic signals in acute posterior circulation cerebral ischemia: sources and consequences. *Stroke*, *43*(3), 747-752. https://doi.org/10.1161/strokeaha.111.633438

Iguchi, Y., Kimura, K., Kobayashi, K., Yamashita, S., Shibazaki, K., & Inoue, T. (2007). Microembolic signals after 7 days but not within 24 hours of stroke onset should be predictor of stroke recurrence. *J Neurol Sci*, *263*(1-2), 54-58. https://doi.org/10.1016/j.jns.2007.05.030

Imam, Y. Z., Chandra, P., Singh, R., Hakeem, I., Al Sirhan, S., Kotob, M.,…Deleu, D. (2024). Incidence, clinical features, and outcomes of posterior circulation ischemic

stroke: insights from a large multiethnic stroke database. *Front Neurol*, *15*, 1302298. https://doi.org/10.3389/fneur.2024.1302298

Kim, J. T., Park, M. S., Choi, K. H., Kim, B. J., Han, M. K., Park, T. H.,…Cho, K. H. (2017). Clinical Outcomes of Posterior Versus Anterior Circulation Infarction With Low National Institutes of Health Stroke Scale Scores. *Stroke*, *48*(1), 55-62. https://doi.org/10.1161/strokeaha.116.013432

King, A., & Markus, H. S. (2009). Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. *Stroke*, *40*(12), 3711-3717. https://doi.org/10.1161/strokeaha.109.563056

Lee, S. J., Hong, J. M., Kim, J. S., & Lee, J. S. (2022). Endovascular Treatment for Posterior Circulation Stroke: Ways to Maximize Therapeutic Efficacy. *J Stroke*, *24*(2), 207-223. https://doi.org/10.5853/jos.2022.00941

Liu, H., Jing, J., Wang, A., Xu, Q., Meng, X., Li, H.,…Wang, Y. (2023). Stroke Recurrence and Antiplatelets in Posterior Versus Anterior Circulation Minor Stroke or Transient Ischemic Attack. *Stroke*, *54*(4), 964-972. https://doi.org/10.1161/strokeaha.122.041738

Lovrencić-Huzjan, A., Demarin, V., Bosnar, M., Vuković, V., & Podobnik-Sarkanji, S. (1999). Color Doppler flow imaging (CDFI) of the vertebral arteries--the normal appearance, normal values and the proposal for the standards. *Coll Antropol*, *23*(1), 175-181.

Oliveira, V., Batista, P., Soares, F., & Ferro, J. M. (2001). HITS in internal carotid dissections. *Cerebrovasc Dis*, *11*(4), 330-334. https://doi.org/10.1159/000047662

Pokharel, Y., Mouhanna, F., Schneider, A. L. C., Rawlings, A. M., Knopman, D. S., Nambi, V.,…Power, M. C. (2019). High-Sensitive Troponin T, Natriuretic Peptide, and Cognitive Change. *J Am Geriatr Soc*, *67*(11), 2353-2361. https://doi.org/10.1111/jgs.16092

Poppert, H., Sadikovic, S., Sander, K., Wolf, O., & Sander, D. (2006). Embolic signals in unselected stroke patients: prevalence and diagnostic benefit. *Stroke*, *37*(8), 2039-2043. https://doi.org/10.1161/01.STR.0000231644.47325.aa

Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). (1998). *Lancet*, *351*(9113), 1379-1387.

Ringelstein, E. B., Droste, D. W., Babikian, V. L., Evans, D. H., Grosset, D. G., Kaps, M.,…Siebler, M. (1998). Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke*, *29*(3), 725-729. https://doi.org/10.1161/01.str.29.3.725

Ritter, M. A., Dittrich, R., Thoenissen, N., Ringelstein, E. B., & Nabavi, D. G. (2008). Prevalence and prognostic impact of microembolic signals in arterial sources of embolism. A systematic review of the literature. *J Neurol*, *255*(7), 953-961. https://doi.org/10.1007/s00415-008-0638-8

Roessler, F. C., Kalms, N., Jann, F., Kemmling, A., Ribbat-Idel, J., Stellmacher, F.,…Royl, G. (2021). First approach to distinguish between cardiac and arteriosclerotic emboli of individual stroke patients applying the histological THROMBEX-classification rule. *Sci Rep*, *11*(1), 8433. https://doi.org/10.1038/s41598-021-87584-2

Rundek, T., Di Tullio, M. R., Sciacca, R. R., Titova, I. V., Mohr, J. P., Homma, S., & Sacco, R. L. (1999). Association between large aortic arch atheromas and high-intensity transient signals in elderly stroke patients. *Stroke*, *30*(12), 2683-2686. https://doi.org/10.1161/01.str.30.12.2683

Sheriff, F., Diz-Lopes, M., Khawaja, A., Sorond, F., Tan, C. O., Azevedo, E.,…Castro, P. (2020). Microemboli After Successful Thrombectomy Do Not Affect Outcome but Predict New Embolic Events. *Stroke*, *51*(1), 154-161. https://doi.org/10.1161/strokeaha.119.025856

Sidhu, P. S. (2000). Ultrasound of the carotid and vertebral arteries. *Br Med Bull*, *56*(2), 346-366. https://doi.org/10.1258/0007142001903265

Telman, G., Sprecher, E., & Kouperberg, E. (2011). Potential relevance of low-intensity microembolic signals by TCD monitoring. *Neurol Sci*, *32*(1), 107-111. https://doi.org/10.1007/s10072-010-0429-8

Zhang, C., Qu, S., Li, H., Li, G., Chen, G., Wang, J., & Wu, C. (2009). Microembolic signals and carotid plaque characteristics in patients with asymptomatic carotid

stenosis. *Scand Cardiovasc J*, *43*(5), 345-351. https://doi.org/10.1080/14017430802699232

ANEXO

DECLARAÇÃO

Eu, **Juliana Patrícia Figueiras Ferreira**, Investigadora Principal do estudo intitulado *"Técnicas avançadas de Doppler transcraniano para a predição e compreensão do declínio cognitivo na doença vascular cerebral"*, aprovado pela Comissão de Ética do Centro Hospitalar Universitário de São João (Parecer n.º 323/2020), declaro que **autorizo o Gilberto Agostinho Magalhães Pereira** a utilizar o referido parecer da Comissão de Ética, bem como a aceder e analisar os dados recolhidos no âmbito deste projeto.

Esta autorização é concedida no respeito pelos princípios éticos e de confidencialidade aplicáveis, mantendo-se inalterada a responsabilidade da Investigadora Principal perante a Comissão de Ética do CHUSJ.

Belval, 25 de setembro de 2025

Juliana Patrícia Figueiras Ferreira
(Investigadora Principal)

Unidade de Investigação

De acordo com o esclarecimento da investigadora nada a opor. À DC.

05 de Novembro de 2020

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

n.º 303/2020

SÃO JOÃO

COMISSÃO DE ÉTICA
7/12/20

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

DIRECÇÃO CLÍNICA
2020/12/6

Exmo. Senhor Presidente do Conselho de Administração do Centro Hospitalar de São João

CONSELHO DE ADMINISTRAÇÃO - REUNIÃO DE
Presidente do Conselho de Administração
20.12.12
(Prof. Doutor Fernando Araújo)
Diretora Clínica | Vogal Executivo | Vogal Executivo
(Profª Doutora Maria João Bacelar) | (Enfª Filomena Cardoso) | (Dr. Luís Porto Gomes) | (Dra Sofia Leal)

Nome do Investigador Principal:

Juliana Patrícia Figueiras Ferreira

Título da Investigação:

Técnicas avançadas de doppler transcraniano para a predição e compreensão do declínio cognitivo na doença vascular cerebral

Pretendendo realizar no(s) Serviço(s) de:

Neurologia - C. Doença Vascular Cerebral

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 6 *de* Julho *de* 2020 .

assinatura

Centro Hospitalar São João
Centro de Epidemiologia Hospitalar
7/12/2020

CES-IM005-0