Asociación entre la permeabilidad de la barrera hematoencefálica y los cambios en la velocidad de la onda de pulso tras un infarto lacunar

Manuel Jesús Gómez-Choco Cuesta

Complex Hospitalari Universitari Moisès Broggi

Sant Joan Despí

6 de Mayo de 2024

Consorci Sanitari Integral

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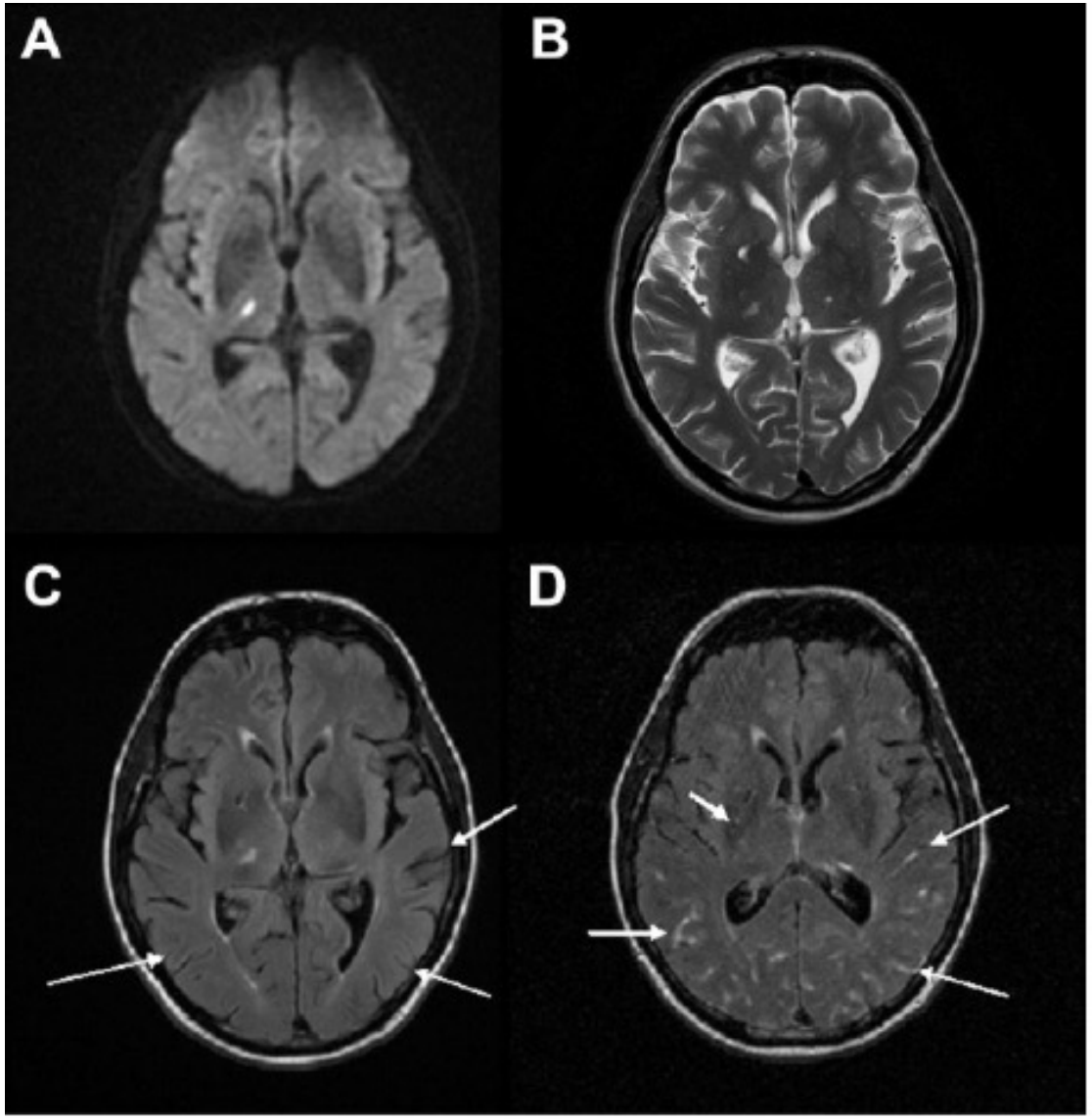
Permeabilidad de BHE
Sistema glinfatico
Hipoperfusión
Estres oxidativo
Inflamación
Enfermedad cerebral de pequeño vaso



Lacunar Stroke Is Associated with Diffuse Blood–Brain Barrier Dysfunction

Joanna M. Wardlaw, MD, FRCR, FRCP, FMedSci,[1] Fergus Doubal, MBChB, MRCP,[1] Paul Armitage, PhD,[1] Francesca Chappell, MSc,[1] Trevor Carpenter, PhD,[1] Susana Muñoz Maniega, PhD,[1] Andrew Farrall, FRCR (Can),[1] Cathie Sudlow, MD, MRCP, PhD,[1] Martin Dennis, FRCP(E),[1] and Baljean Dhillon, FRCS, FRCOphth[2]

Blood-brain barrier leakage hotspots collocating with brain lesions due to sporadic and monogenic small vessel disease

Salvatore Rudilosso[1], Michael S Stringer[2], Michael Thrippleton[2], Francesca Chappell[2], Gordon W Blair[2], Daniela Jaime Garcia[2], Fergus Doubal[2], Iona Hamilton[2], Esther Janssen[3], Anna Kopczak[4], Michael Ingrisch[5], Danielle Kerkhofs[6], Walter H Backes[7], Julie Staals[6], Marco Duering[4,8], Martin Dichgans[4,9,10] and Joanna M Wardlaw[2]; on behalf of the SVDs@target consortium

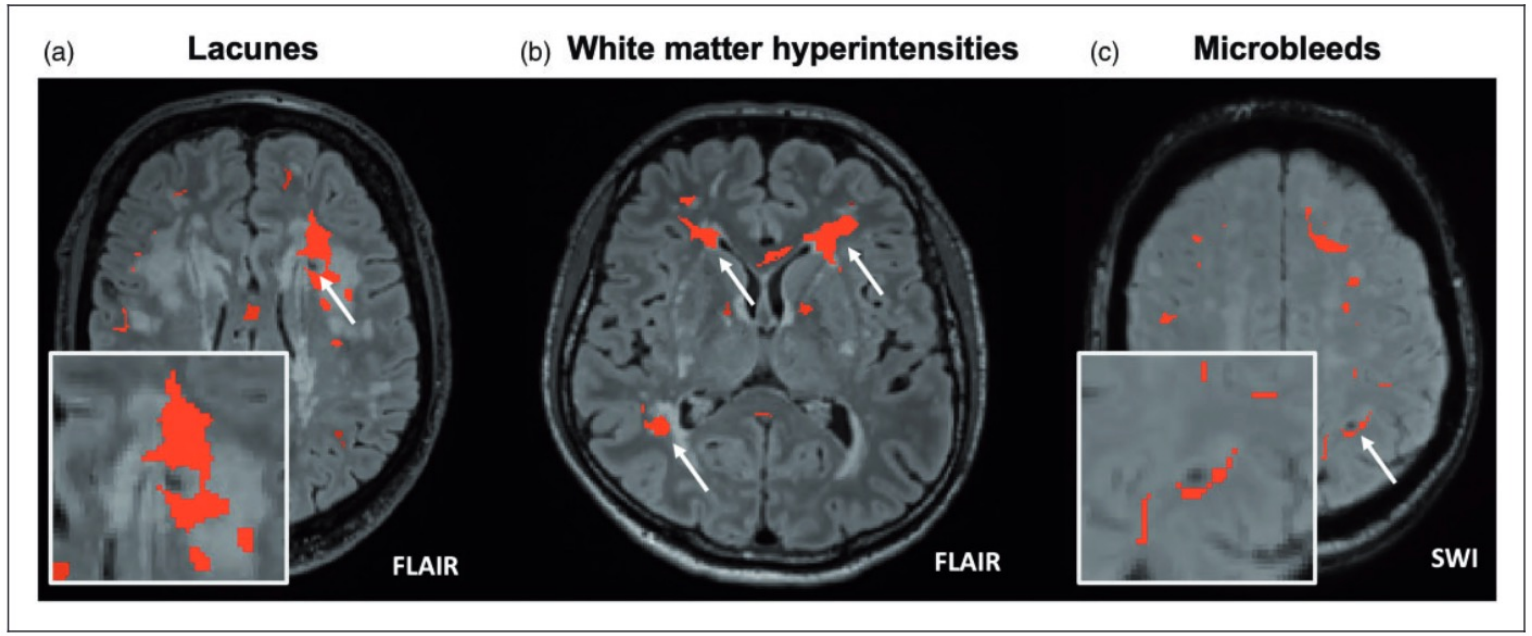


Figure 4. Representative images of hotspots corresponding to each SVD feature.
(a) A lacune in the left anterior periventricular region is surrounded by a hotspot. (b) WMH areas with hotspots within or at the edges and (c) A lobar cerebral microbleed in the left parieto-frontal lobe is at edges of a hotspot.

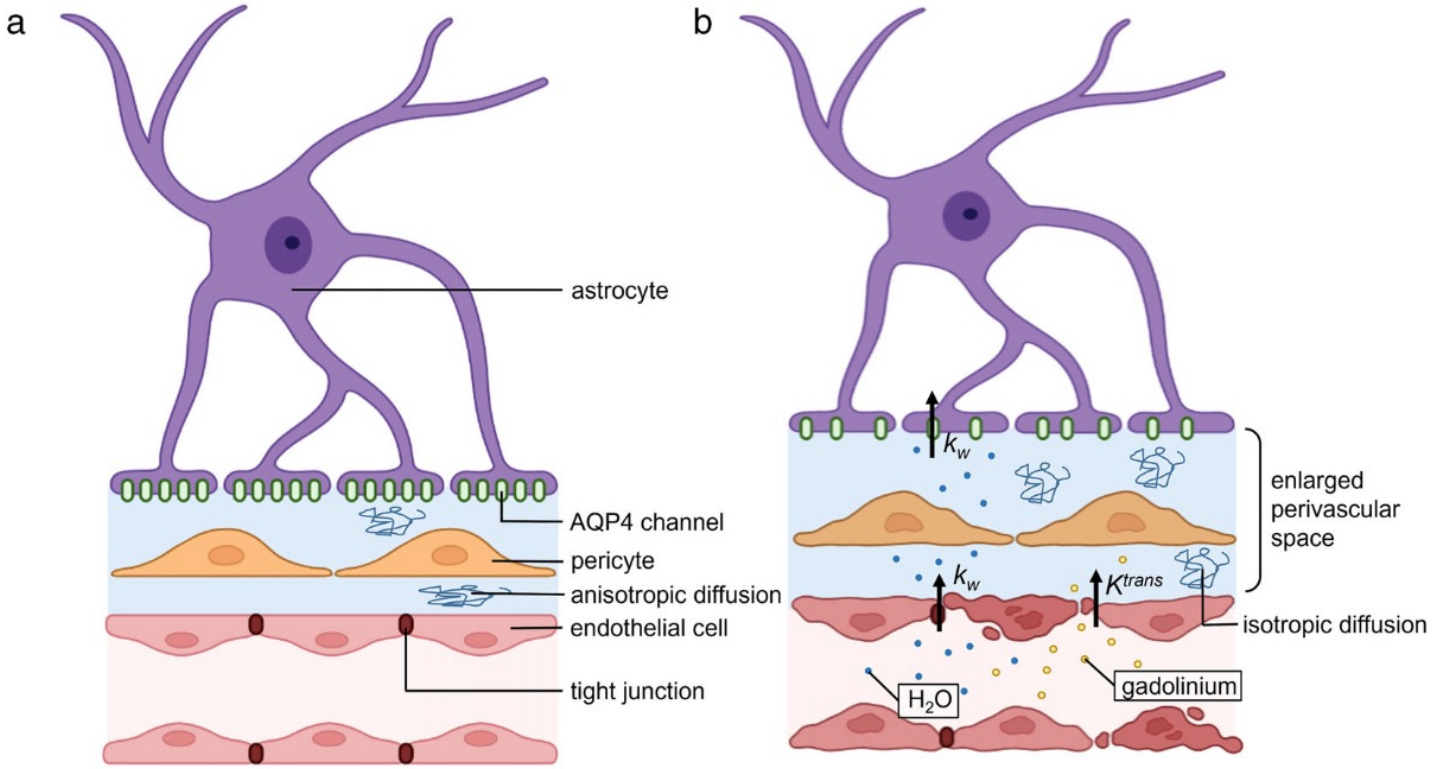
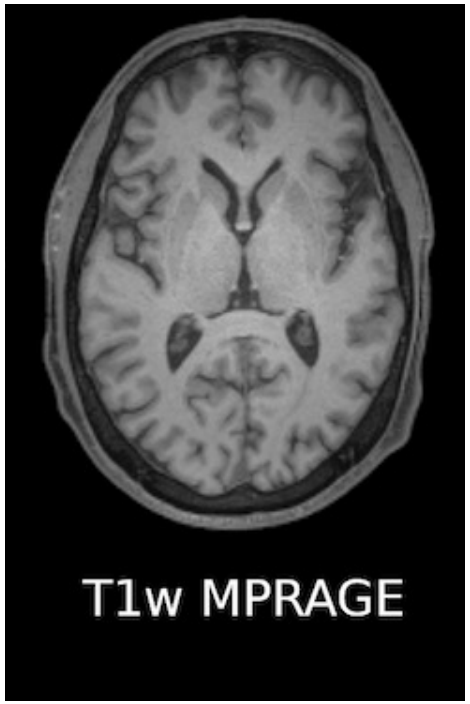
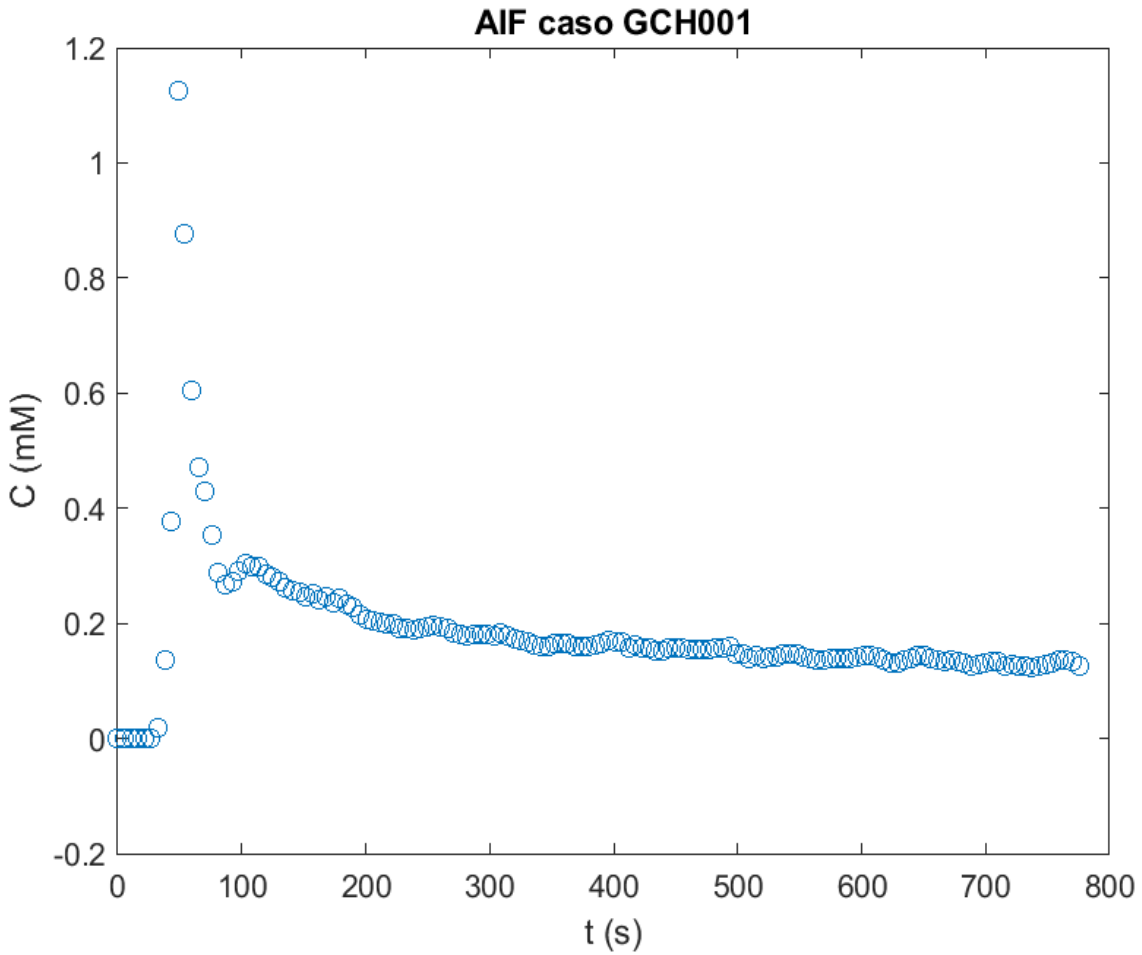


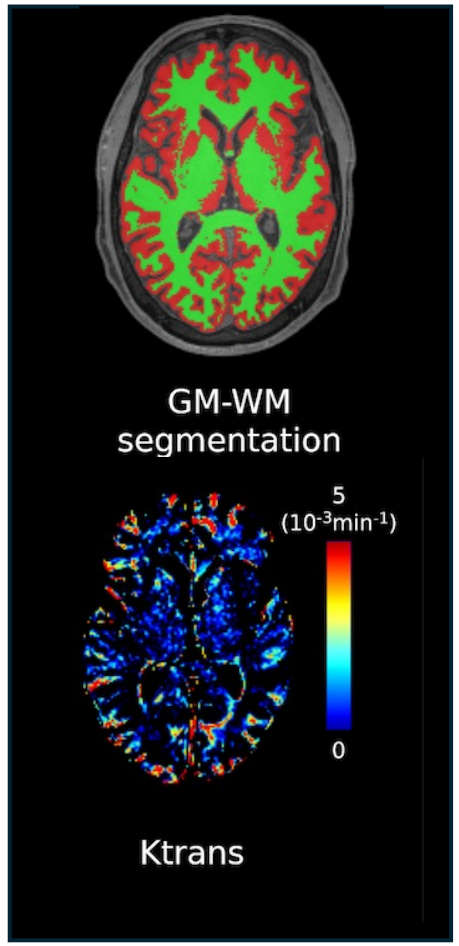
TABLE 2. MRI Methods to Measure BBB Disruption

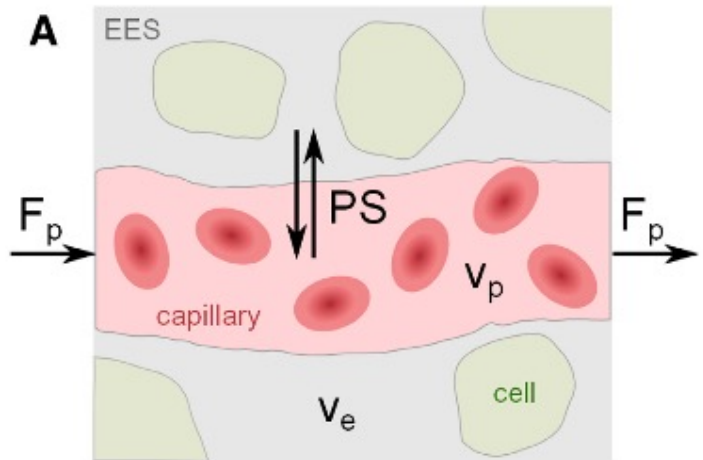
MRI method	Sensitive to	BBB-related measures
DCE MRI	Extravasation of gadolinium chelates over the BBB	BBB leakage rate K^{trans} or K_i (minute^{-1})
		Volume fraction of the leaking brain tissue[24] (%)
		BBB hotspot volume fraction[25] (%)
ASL	Water exchange across the BBB	Water exchange rate k_w (minute^{-1})

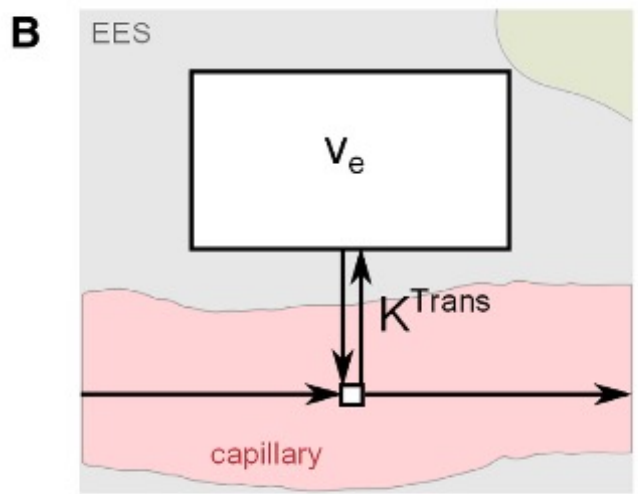
Abbreviations: BBB, blood–brain barrier; DCE, dynamic contrast-enhanced; MRI, magnetic resonance imaging; ASL, arterial spin labeling.

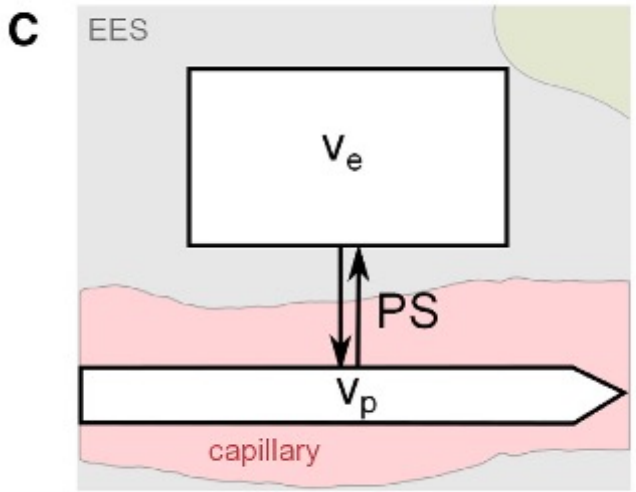

T1w MPRAGE


AIF caso GCH001
C (mM)
t (s)
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
0
100
200
300
400
500
600
700
800


GM-WM
segmentation
5
(10-3min-1)
0
Ktrans


A
EES
PS
F_p
F_p
v_p
capillary
cell
v_e


B
EES
v_e
K^{Trans}
capillary


C
EES
v_e
PS
v_p
capillary

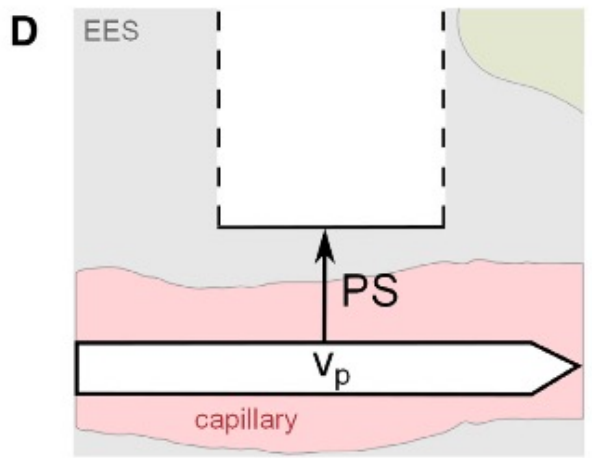

D
EES
PS
v_p
capillary

Table 2
Summary of the main HARNESS consensus recommendations for implementation and future development of BBB leakage imaging

Category	Recommendations	Research questions and objectives
MRI hardware	• 1.5 T or 3 T • Head coil with high sensitivity and homogeneity • Maximal temporal stability in signal and B_1 • Padding to restrict head motion • QA program including "sham" DCE-MRI without contrast in volunteers	• Influence of field strength on precision • Application/development of motion reduction/ compensation techniques
Pulse sequence	• 3D spoiled gradient echo or 3D saturation-recovery spoiled gradient echo • Reliable pre-injection T_1 measurement	• Effect on precision • Influence of flip angle inhomogeneity • Artifact reduction
Acquisition parameters	• Spatial resolution sufficient to determine VIF and smallest structures of interest without partial volume artifact • Temporal resolution 1 min or better • 15-20 minute DCE-MRI acquisition time	• Influence of sequence parameters and injection protocol on precision and accuracy
Contrast agent	• Standard dose of low–molecular weight GBCA • Selection based on latest appropriate (e.g., EMA/ FDA) safety guidance	• Novel, safe contrast agents with greater T_1 relaxivity and BBB permeability • Development and validation of non-exogenous contrast methods
Preprocessing	• Spatial realignment of time series • Signal-concentration conversion, using pre-contrast T_1 measurement if available	• Utility of flip angle correction • Influence of water exchange rates • Tissue dependence of relaxivity
Pharmacokinetic modeling	• Fit time-concentration data to appropriate pharmacokinetic (typically Patlak) model	• Causes and correction of signal drift • Spatiotemporal noise structure
Vascular input function	• Measurement of individual patient VIF in a large venous sinus	• Evaluation of signal phase for estimating VIF
Regional measurement	• Report representative *PS* (K^{Trans}) measurements for each region or tissue • Minimize cross-contamination between tissues due to partial volume artifact and image misregistration	• Development and validation of postprocessing methods to reduce influence of noise and artifact in parameter maps
Biological interpretation and reporting	• K^{Trans} or *PS* reported as "leakage rate" of the GBCA • Full reporting of DCE-MRI and T_1 measurement acquisition and analysis (Table 3)	• Data on precision and accuracy of *PS* including validation against other measures of BBB integrity • Reliable measurement of capillary surface area in vivo

Abbreviations: BBB, Blood-brain barrier; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; GBCA, gadolinium-based contrast agent; K^{Trans}, volume transfer constant; *PS*, permeability–surface area product; VIF, vascular input function.

Review Article

Quantifying blood-brain barrier leakage in small vessel disease: Review and consensus recommendations

Michael J. Thrippleton[a,b,c,*], Walter H. Backes[d], Steven Sourbron[e], Michael Ingrisch[f], Matthias J. P. van Osch[g], Martin Dichgans[h], Franz Fazekas[i], Stefan Ropele[i], Richard Frayne[j,k,l], Robert J. van Oostenbrugge[m], Eric E. Smith[j,k], Joanna M. Wardlaw[a,b,c]

Blood-brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort study

Joanna M. Wardlaw[a,*], Stephen J. Makin[a], Maria C. Valdés Hernández[a], Paul A. Armitage[b], Anna K. Heye[a], Francesca M. Chappell[a], Susana Muñoz-Maniega[a], Eleni Sakka[a], Kirsten Shuler[a], Martin S. Dennis[a], Michael J. Thrippleton[a]

[a]*Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK*
[b]*Academic Unit of Radiology, Department of Cardiovascular Science, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK*

Table 2
Association between BBB leakage, vascular risk factors, and brain parameters: hypertension, mean arterial pressure, smoker status, brain tissue T1 signal precontrast, and intravascular signal (sagittal sinus), adjusted for one another, age, and combined Fazekas score

Tissue	Variable	β coefficient × 10^3	95% CI × 10^3	*P*-value
Normal-appearing white matter	Hypertension	0.206	0.118, 0.295	<.0001
	Mean arterial pressure	−0.00105	−0.0036, 0.0015	.41
	Pulse pressure	0.00121	−0.00061, 0.0030	.19
	Smoking status	−0.050	−0.130, 0.026	.18
	Tissue T1	0.46	0.153, 0.768	.0033
	Intravascular contrast	0.050	−0.080, 0.181	.45
Deep gray matter	Hypertension	0.233	0.111, 0.354	.0002
	Mean arterial pressure	0.00017	−0.0033, 0.0036	.93
	Pulse pressure	0.00380	0.0013, 0.0063	.003
	Smoking status	0.035	−0.080, 0.146	.53
	Tissue T1	0.365	−0.0018, 0.732	.051
	Intravascular contrast	0.00062	−0.180, 0.182	.99
CSF	Hypertension	0.338	0.016, 0.66	.040
	Mean arterial pressure	0.016	0.0064, 0.025	.0009
	Pulse pressure	0.017	0.011, 0.024	<.0001
	Smoking status	−0.30	−0.590, −0.010	.042
	Tissue T1	1.107	0.903, 1.31	<.0001
	Intravascular contrast	1.363	0.878, 1.848	<.0001
WMH	Hypertension	0.256	0.131, 0.38	<.0001
	Mean arterial pressure	0.000368	−0.0032, 0.0039	.84
	Pulse pressure	0.00333	0.00076, 0.00589	.011
	Smoking status	−0.110	−0.23, 0.0002	.050
	Tissue T1	0.536	0.163, 0.909	.0049
	Intravascular contrast	0.237	0.052, 0.423	.012
Index infarct	Hypertension	0.677	0.444, 0.91	<.0001
	Mean arterial pressure	−0.00298	−0.009, 0.003	.35
	Pulse pressure	−0.00203	−0.0066, 0.0025	.38
	Smoking status	−0.040	−0.240, 0.154	.67
	Tissue T1	1.617	1.249, 1.984	<.0001
	Intravascular contrast	−0.040	−0.390, 0.305	.81
Old infarct	Hypertension	0.472	0.208, 0.735	.0005
	Mean arterial pressure	0.016	0.007, 0.024	.0002
	Pulse pressure	0.00261	−0.0033, 0.0085	.39
	Smoking status	−0.40	−0.64, −0.16	.001
	Tissue T1	0.773	0.317, 1.228	.001
	Intravascular contrast	0.086	−0.330, 0.499	.68

Abbreviations: BBB, blood-brain barrier; CI, confidence interval; CSF, cerebrospinal fluid; WMH, white matter hyperintensities.

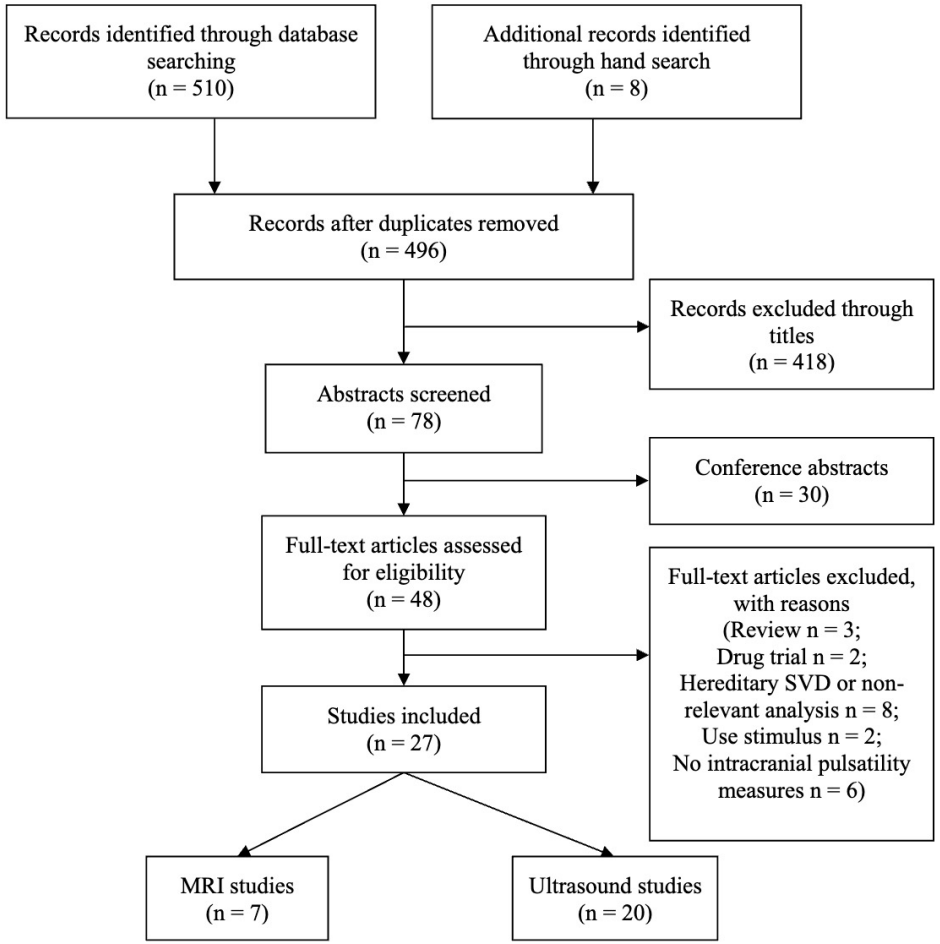
Tracer kinetic assessment of blood–brain barrier leakage and blood volume in cerebral small vessel disease: Associations with disease burden and vascular risk factors

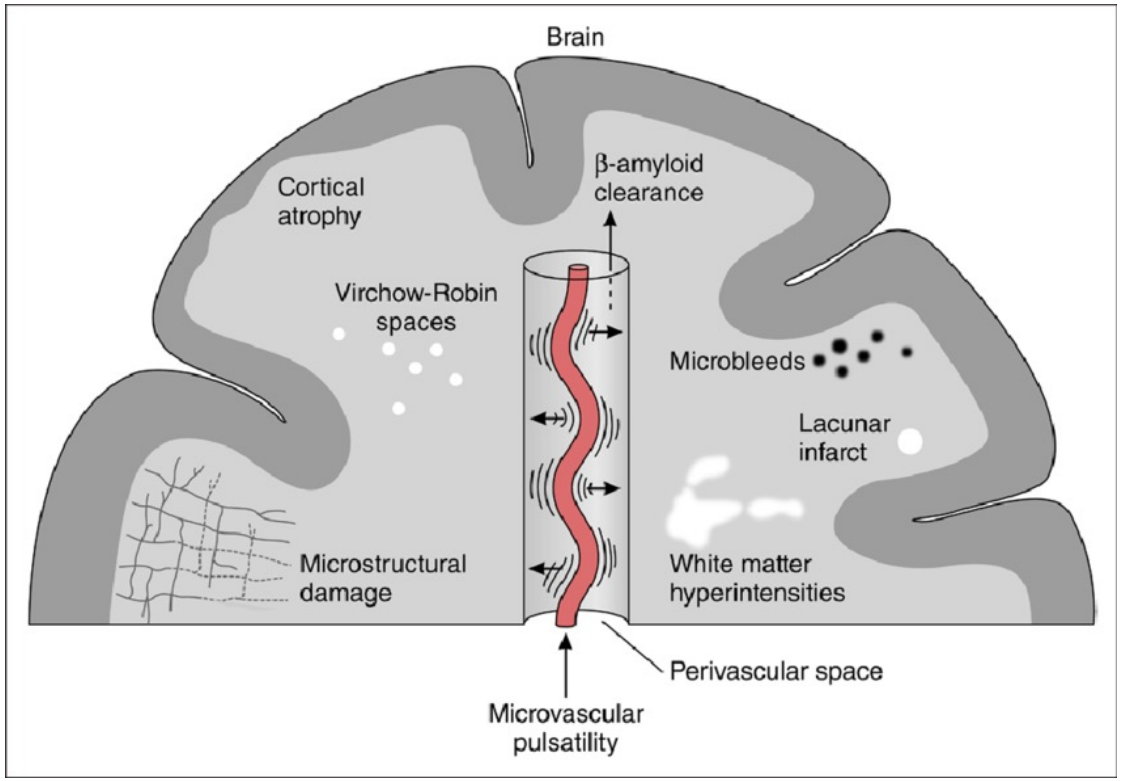
Michael S. Stringer[a,b], Anna K. Heye[a,c], Paul A. Armitage[d], Francesca Chappell[a,b], Maria del C. Valdés Hernández[a,b], Stephen D.J. Makin[e], Eleni Sakka[a,b], Michael J. Thrippleton[a,b,*], Joanna M. Wardlaw[a,b]

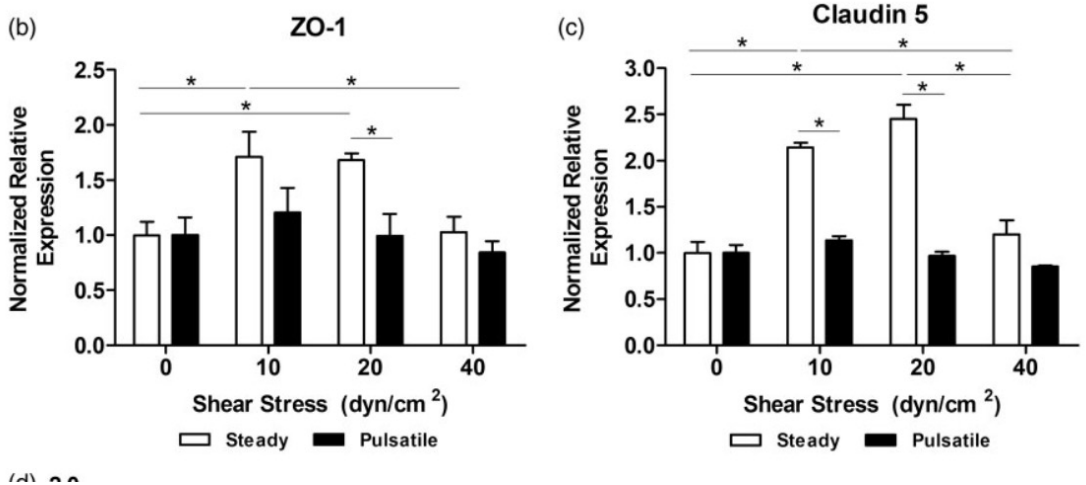
201 patients with non-disabling ischemic stroke.
DCE-MRI1 to 3 months post-stroke.

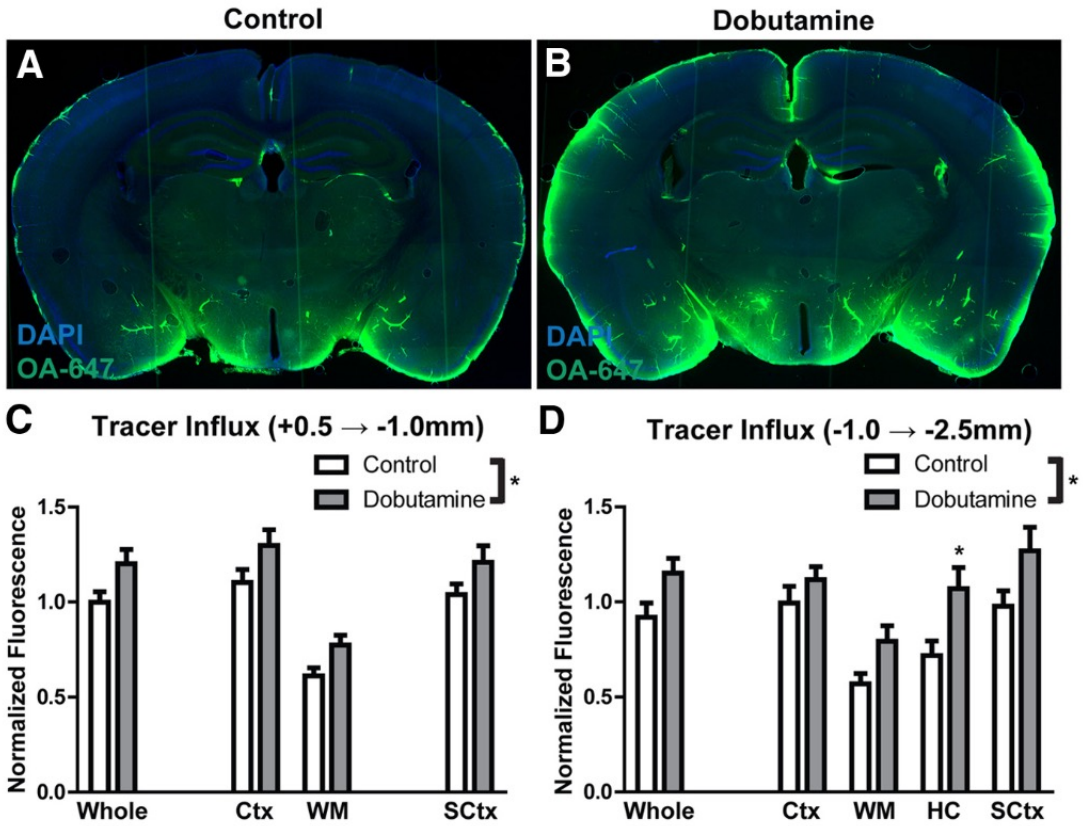
Table 2
Permeability surface area (*PS*, 10^{-4} min^{-1}) against age (years), Fazekas score, stroke subtype, mean arterial pressure (mmHg), hypertension status, pulse pressure (mmHg) and smoking status in each tissue type of interest. (WM = white matter, CI = confidence interval, MAP = mean arterial pressure).

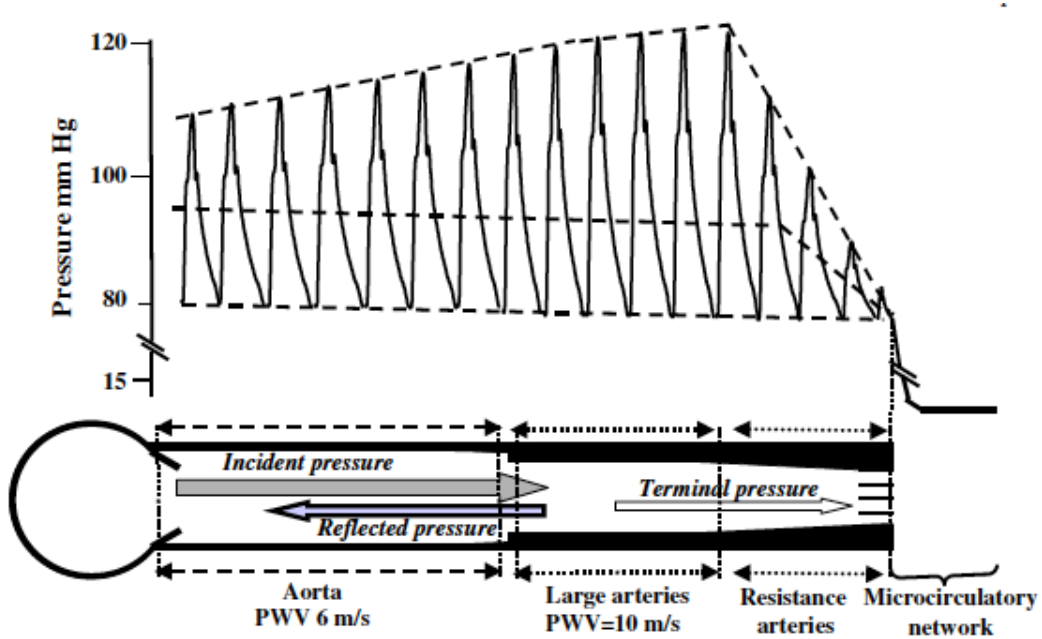
	Tissue *PS* associations using Fazekas score			
Tissue	Variable	B coefficient	95% CI	p-value
Normal appearing WM	Age	−0.044	−0.070 to −0.018	*<0.001*
	Fazekas score	0.150	−0.008 to 0.308	*0.062*
	Stroke subtype	−0.398	−0.868 to 0.072	*0.097*
	MAP	−0.006	−0.023 to 0.011	0.500
	Hypertension	0.411	−0.141 to 0.963	0.144
	Pulse pressure	0.004	−0.009 to 0.017	0.562
	Smoking status	−0.423	−0.942 to 0.096	0.109
WM Hyperintensities	Age	−0.030	−0.058 to −0.002	*0.035*
	Fazekas score	0.092	−0.081 to 0.265	0.296
	Stroke subtype	−0.039	−0.550 to 0.473	0.882
	MAP	0.002	−0.017 to 0.021	0.862
	Hypertension	0.309	−0.294 to 0.912	0.314
	Pulse pressure	0.002	−0.013 to 0.016	0.810
	Smoking status	−0.028	−0.594 to 0.537	0.922
Grey matter	Age	−0.044	−0.068 to −0.019	*<0.001*
	Fazekas score	0.150	0.001 to 0.299	*0.049*
	Stroke subtype	−0.285	−0.729 to 0.159	0.207
	MAP	−0.004	−0.020 to 0.013	0.650
	Hypertension	0.207	−0.315 to 0.729	0.434
	Pulse pressure	0.010	−0.002 to 0.023	0.103
	Smoking status	0.148	−0.343 to 0.638	0.553
Recent stroke lesion	Age	0.019	−0.067 to 0.105	0.666
	Fazekas score	−0.067	−0.596 to 0.461	0.801
	Stroke subtype	−2.017	−3.621 to −0.413	*0.014*
	MAP	0.027	−0.032 to 0.086	0.366
	Hypertension	2.195	0.194 to 4.197	*0.032*
	Pulse pressure	−0.020	−0.064 to 0.025	0.385
	Smoking status	0.774	−0.965 to 2.514	0.380

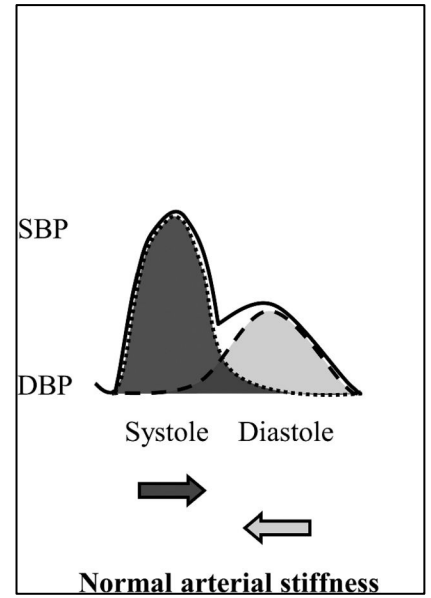

Records identified through database searching (n = 510)
Additional records identified through hand search (n = 8)
Records after duplicates removed (n = 496)
Records excluded through titles (n = 418)
Abstracts screened (n = 78)
Conference abstracts (n = 30)
Full-text articles assessed for eligibility (n = 48)
Full-text articles excluded, with reasons (Review n = 3; Drug trial n = 2; Hereditary SVD or non-relevant analysis n = 8; Use stimulus n = 2; No intracranial pulsatility measures n = 6)
Studies included (n = 27)
MRI studies (n = 7)
Ultrasound studies (n = 20)

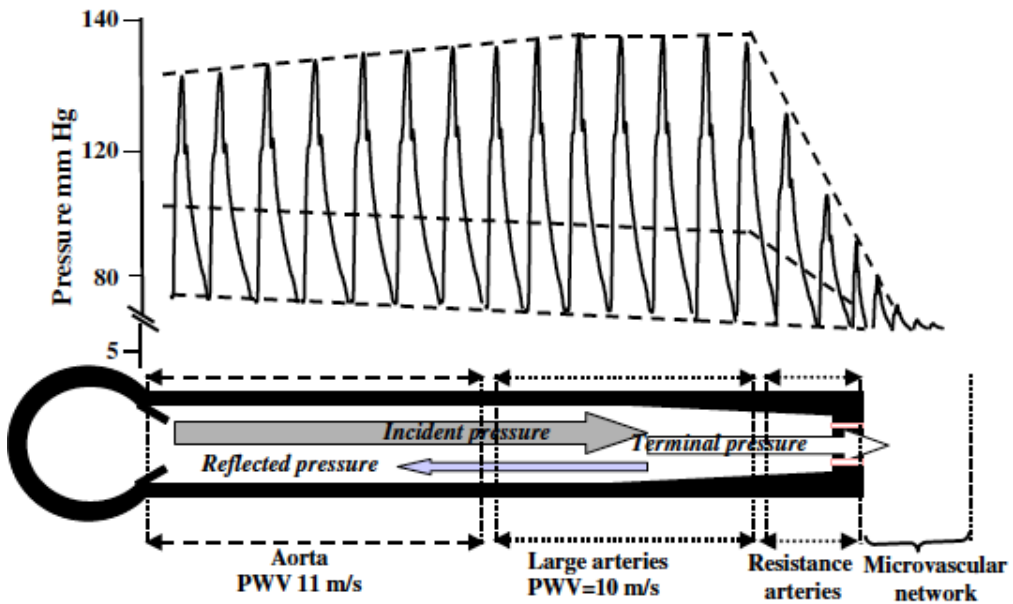

Brain
Cortical atrophy
β-amyloid clearance
Virchow-Robin spaces
Microbleeds
Lacunar infarct
Microstructural damage
White matter hyperintensities
Perivascular space
Microvascular pulsatility


(b)
ZO-1
Normalized Relative Expression
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
40
Shear Stress (dyn/cm 2)
Steady
Pulsatile
(c)
Claudin 5
Normalized Relative Expression
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
40
Shear Stress (dyn/cm 2)
Steady
Pulsatile


Control
Dobutamine
A
B
DAPI
OA-647
DAPI
OA-647
C
Tracer Influx (+0.5 → -1.0mm)
Control
Dobutamine
*
Normalized Fluorescence
1.5
1.0
0.5
0.0
Whole
Ctx
WM
SCtx
D
Tracer Influx (-1.0 → -2.5mm)
Control
Dobutamine
*
Normalized Fluorescence
1.5
1.0
0.5
0.0
*
Whole
Ctx
WM
HC
SCtx


120
100
80
15
Pressure mm Hg
Incident pressure
Terminal pressure
Reflected pressure
Aorta
PWV 6 m/s
Large arteries
PWV=10 m/s
Resistance
arteries
Microcirculatory
network


SBP
DBP
Systole
Diastole
Normal arterial stiffness


140
120
80
5
Pressure mm Hg
Incident pressure
Terminal pressure
Reflected pressure
Aorta
PWV 11 m/s
Large arteries
PWV=10 m/s
Resistance
arteries
Microvascular
network

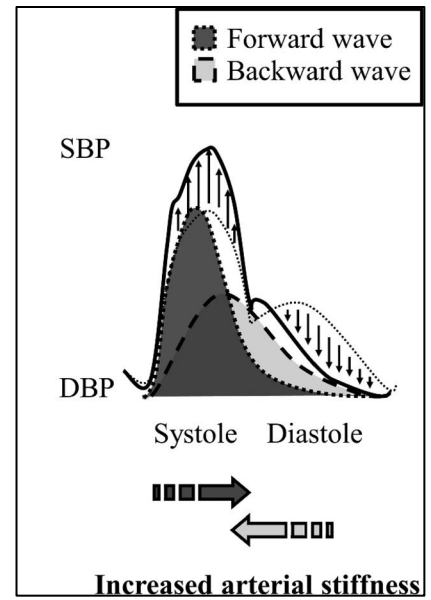
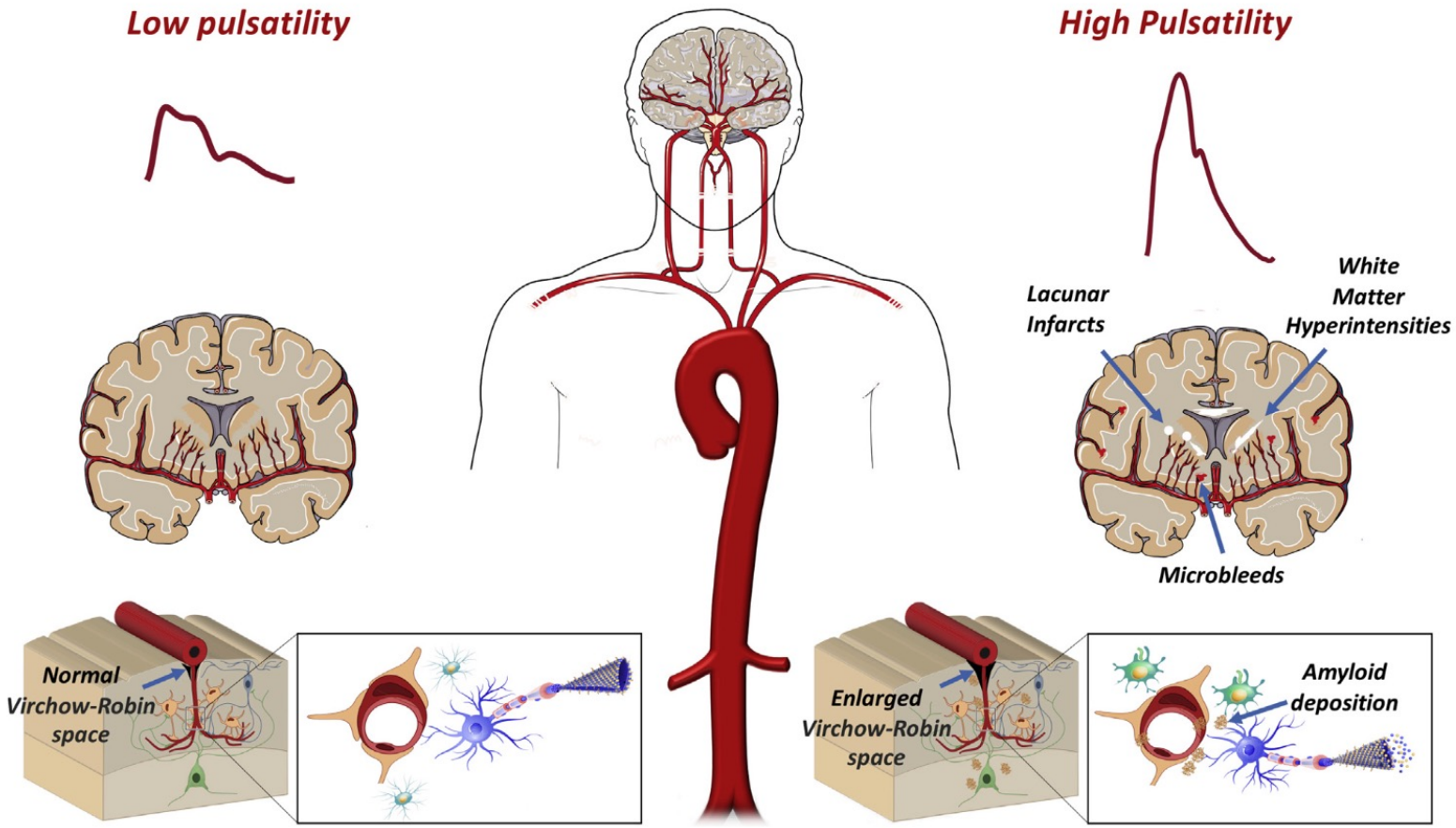
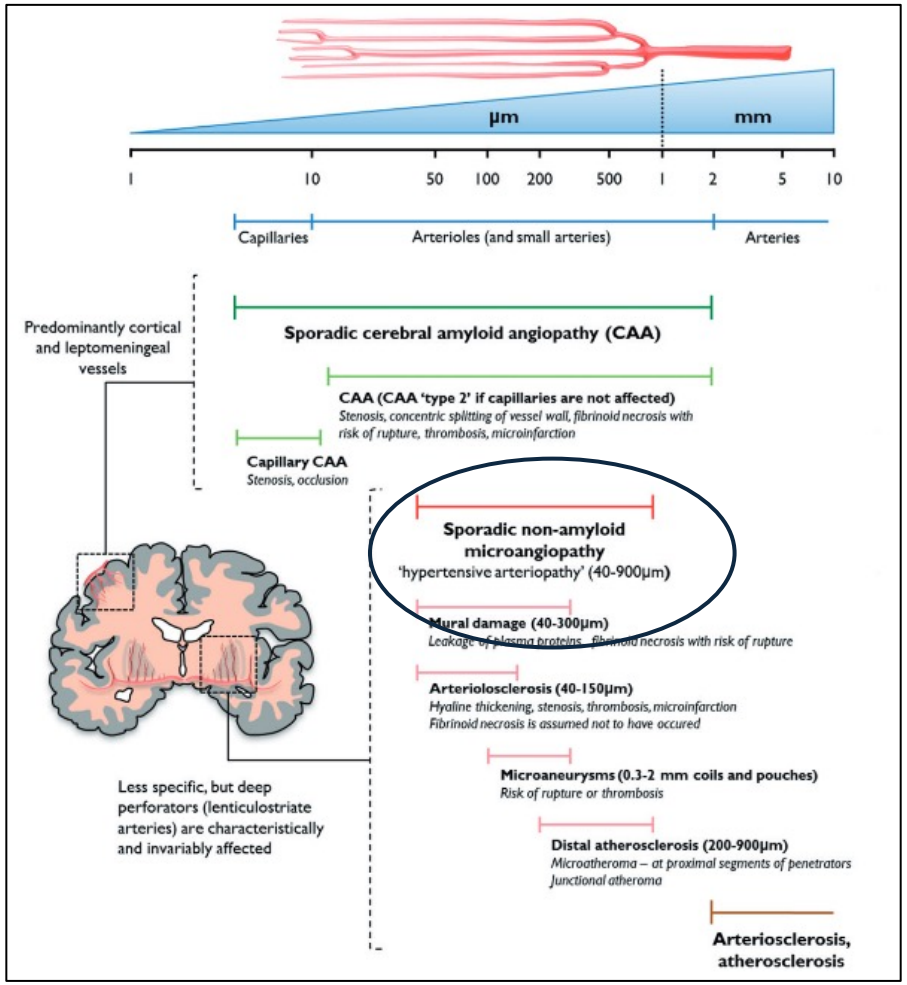
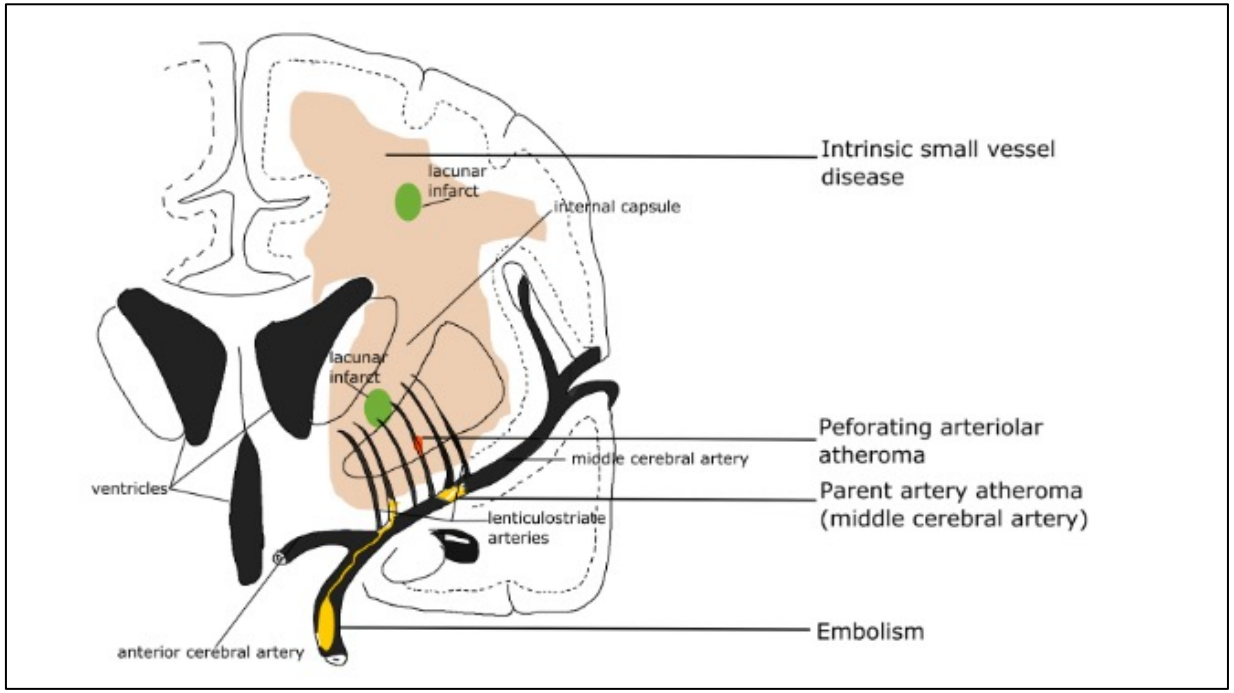

Forward wave
Backward wave
SBP
DBP
Systole
Diastole
Increased arterial stiffness

FIGURE 7 Arterial Stiffness and Age-Related Changes in the Brain Commonly Seen in Alzheimer Disease and Related Dementias





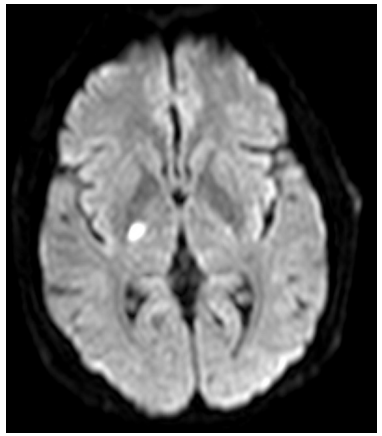
PI 17/1188
Rigidez Arterial Ictus Lacunar

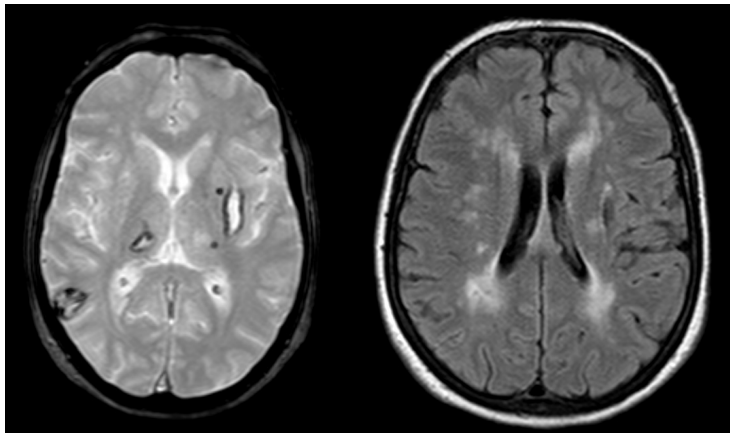


1. Pacientes mayores de 18 años.
2. mRS(modified Rankin Scale) ≤ 3 en la inclusión
3. Diagnóstico de ictus lacunar agudo confirmado mediante RM cerebral.
4. Dentro de los 7 y 30 días posteriores al ictus

Inclusión

2 años



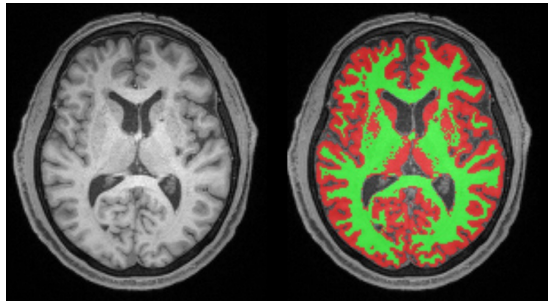


103 pacientes

3 abandonos
4 fallecimientos
4 perdidas seguimiento

92 pacientes RM análisis final

29 pacientes

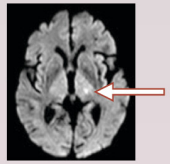


EUROPEAN STROKE JOURNAL

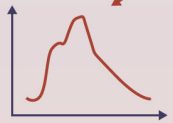
Relationship of arterial stiffness and baseline vascular burden with new lacunes and microbleeds: a longitudinal cohort study

Is pulse wave velocity (PWV) associated with the development of new lacunes or microbleeds in patients with a recent small subcortical infarct (RSSI)?

Methods



Patients with RSSI n = 92



PWV

Cerebral small vessel disease (cSVD) score

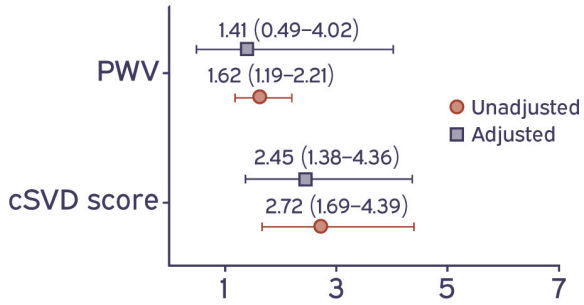
Assessment of **new lacunes** or **microbleeds** 2 years later

Results

New lacunes or microbleeds

25 patients (**27%**)

Association of PWV and cSVD score with new lacunes or microbleeds



Conclusion

After adjustment for age, NT-proBNP and hypercholesterolemia **PWV** was not associated with new lacunes or microbleeds, but **cSVD score** was.

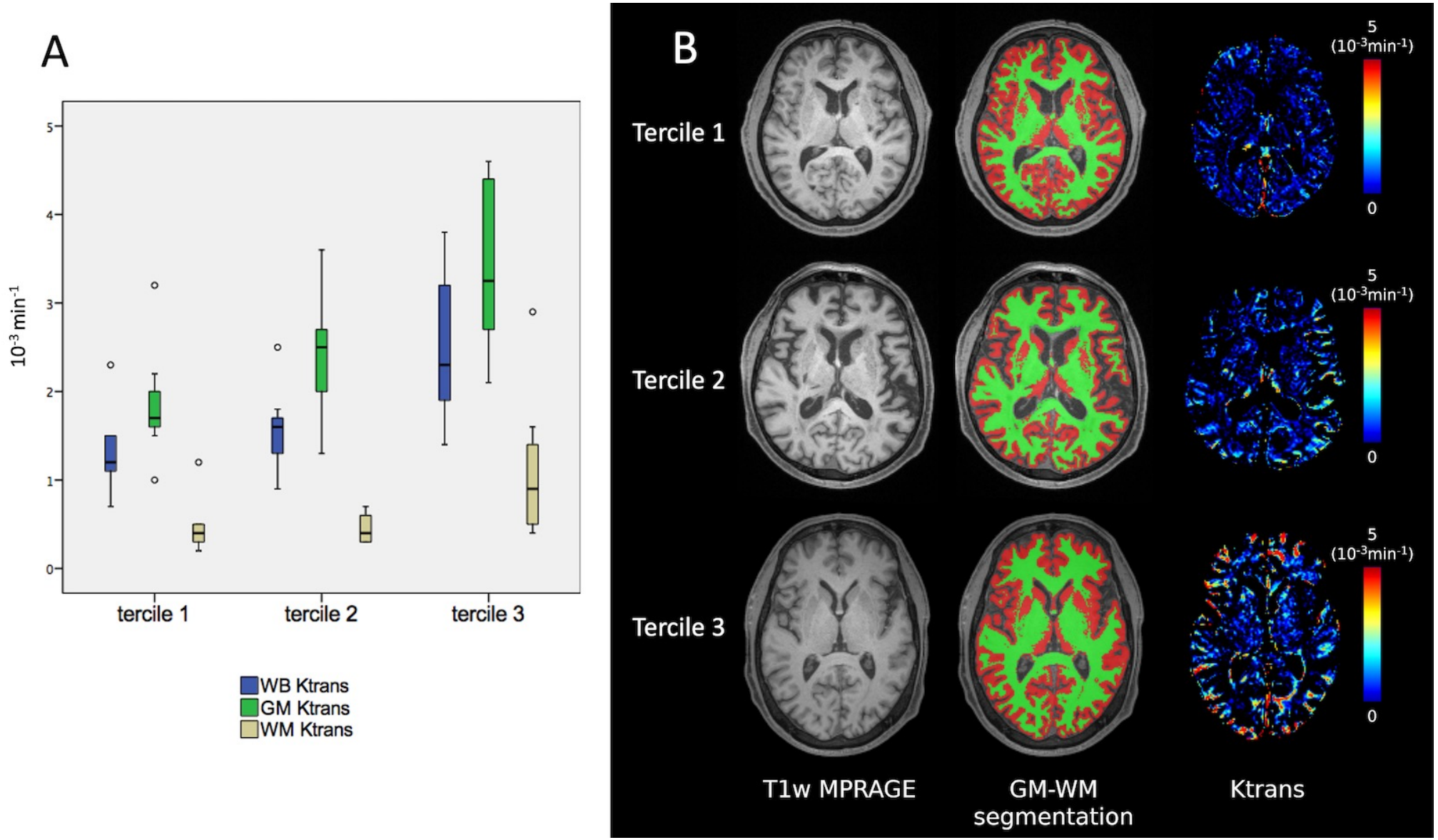
Mena, L., et al. European Stroke Journal, 2023 mgomezch@csi.cat doi.org/10.1177_23969873231207764

Characteristics	All patients (n=29)
Age, years	66.7(9.7)
Sex, male	24 (83)
BMI	29.2 (3.4)
Hypertension	22 (76)
Diabetes	9 (31)
Hypercholesterolemia	12 (41)
Tobacco use	
-Current	6 (21)
-Previous (≥ 1 year)	10 (35)
Ischemic heart disease	1 (3)
NT-proBNP, pg/ml	52 (24-108)
UAE ≥30 mg/g	6 (20)
24-h SBP, mm Hg	128.7 (11.9)
24-h DBP, mm Hg	78.4 (8.7)
24-h PWV, m/s	9.6 (1.5)
cSVD score	2 (1-3)

	WB-Ktrans (n=29)	GM-Ktrans (n=29)	WM-Ktrans (n=29)
Age	0.322, p=0.083	0.327, p=0.077	0.352, p=0.056
24-h SBP	-0.082, p=0.666	-0.145, p=0.446	0.023, p=0.905
24-h DBP	0.147, p=0.439	0.085, p=0.655	0.198, p=0.295
24-h PWV	0.110, p=0.563	0.117, p=0.539	0.188, p=0.320
NT-proBNP	0.067, p=0.751	0.079, p=0.706	0.115, p=0.585
UAE	-0.158, p=0.406	-0.178, p=0.346	-0.107, p=0.574

	WB-Ktrans(n=29)	GM-ktrans(n=29)	WM-Ktrans(n=29)
Δ24-h SBP	-0.255, p=0.175	-0.276, p=0.139	-0.133, p=0.482
Δ24-h DBP	-0.142, p=0.453	-0.166, p=0.379	-0.021, p=0.911
Δ24-h PWV	0.651, p<0.001	0.657, p<0.001	0.530, p=0.003
ΔNT-proBNP	-0.134, p=0.524	-0.192, p=0.358	-0.042, p=0.844
ΔUAE	-0.035, p=0.856	-0.054, p=0.782	-0.026, p=0.894

	1st tercile (n=9)	2nd tercile (n=10)	3rd tercile (n=10)	P value
Age, years	61.9 (10.0)	67.2 (8.9)	70.5 (9.2)	0.153
Sex, male	9 (100)	6 (60)	9 (90)	**0.053**
BMI	28.9 (3.2)	27.3 (3.4)	31.3 (2.7)	**0.029**
Hypertension	5 (56)	8(80)	9(90)	0.201
Diabetes	5(56)	3(30)	1(10)	0.100
Hypercholesterolemia	6(67)	4(40)	2(20)	0.119
Baseline 24-h SBP, mm Hg	135.6 (14.0)	124.8 (9.9)	126.3 (10.1)	0.140
Baseline 24-h DBP, mm Hg	83.8 (11.0)	74.3 (6.7)	77.8 (6.2)	0.096
Baseline NT-proBNP, pg/ml	37.5 (20-237)	60(42-165)	50(21-105)	0.632
Baseline UAE≥30 mg/g	2 (22)	1 (10)	3 (30)	0.539
Δ 24-h SBP, mm Hg	15.2 (10.7)	2.9 (4.3)	-4.5 (14.4)	**0.004**
Δ 24-h DBP, mm Hg	9.33(8.56)	2.0(5.06)	4.21(8.77)	**0.035**
Δ NT-proBNP, pg/ml	37.2 (141.5)	9.6 (69.0)	-25.9 (58.8)	0.137
Δ UAE, mg/g	3.1 (14.1)	12.7 (106.4)	-15.1 (25.9)	0.293
cSVD score	2 (0-2)	2 (1-3)	2 (1-2)	0.579
RSSI size, mm	10.5(5.3-15.4)	10.1(8.4-14.2)	8.8(7.1-12.2)	0.784
Fazekas	3(1-3)	3(2.5-4)	2(2-3)	0.132
Lacunes	5(55.6)	7(70.0)	6(60.0)	0.800
Microbleeds	1(11.1)	3(30.0)	2(20.0)	0.596
BG EPVS	2(1-2)	2(1.8-2.3)	2(1.8-2.3)	0.695
CSO EPVS	2(1.5-3)	1(1-4)	2(1-3)	0.590
WB ktrans, 10^{-3} min^{-1}	1.32 (0.44)	1.58 (0.43)	1.80 (0.74)	**0.002**
GM Ktrans, 10^{-3} min^{-1}	1.87 (0.61)	2.39 (0.61)	3.37 (0.91)	**0.001**
WM Ktrans, 10^{-3} min^{-1}	0.48 (0.29)	0.46 (0.15)	1.07 (0.76)	**0.014**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tercile 1
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WB Ktrans
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T1w MPRAGE
GM-WM segmentation
Ktrans

	Unadjusted	Model 1*	Model 2**	Model 3***
WB-Ktrans	0.683 (0.411-1.013) p<0.001	0.708 (0.398-1.078) P<0.001	0.725 (0.384-1.127) P<0.001	0.707 (0.370-1.103) P<0.001
GM-Ktrans	0.619 (0.414-1.244) P<0.001	0.637 (0.375-1.332) p=0.001	0.629 (0.316-1.369) p=0.003	0.643 (0.351-1.371) p=0.002
WM-Ktrans	0.745 (0.375-0.785) P<0.001	0.785 (0.383-0.840) p<0.001	0.865 (0.455-0.892) p<0.001	0.772 (0.367-0.834) p<0.001

Table 5. Linear regression models. Correlation between Ktrans values and Δ 24-h PWV

*Adjusted by age at inclusion and sex

**Adjusted by age at inclusion, sex, BMI, and Δ24-h SBP

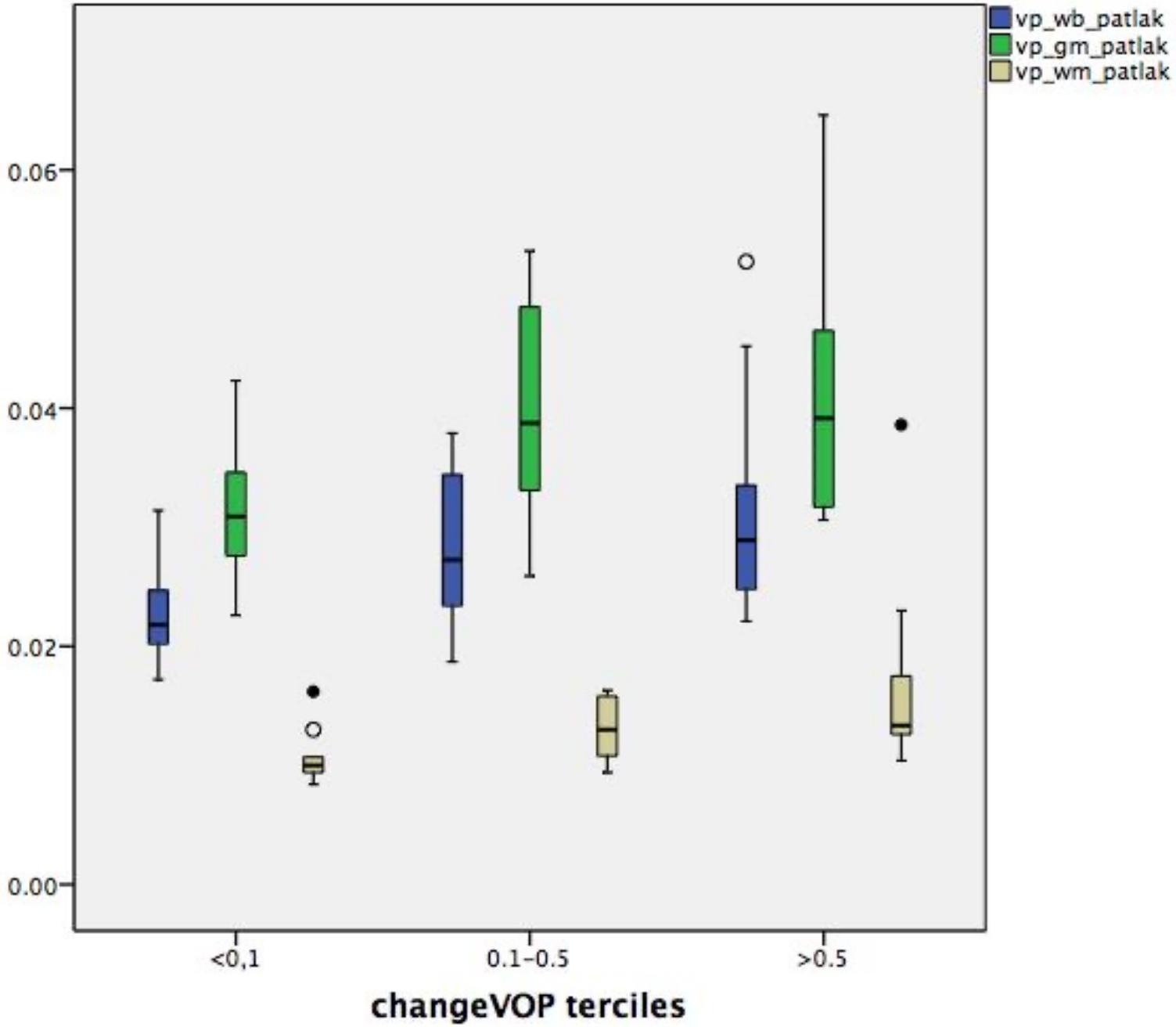
*** Adjusted by age at inclusion, sex, BMI and Δ24-h DBP

- El aumento de permeabilidad de la BHE se asocia con la ECPV
- La rigidez arterial podria contribuir a la disfunción de la BHE
- En nuestro estudio, el aumento de VOP despues de un ictus lacunar se ha asociado con una mayor permeabilidad de la BHE

Muchas gracias

Consorci Sanitari Integral

Amb tu, per la teva salut


vp_wb_patlak
vp_gm_patlak
vp_wm_patlak
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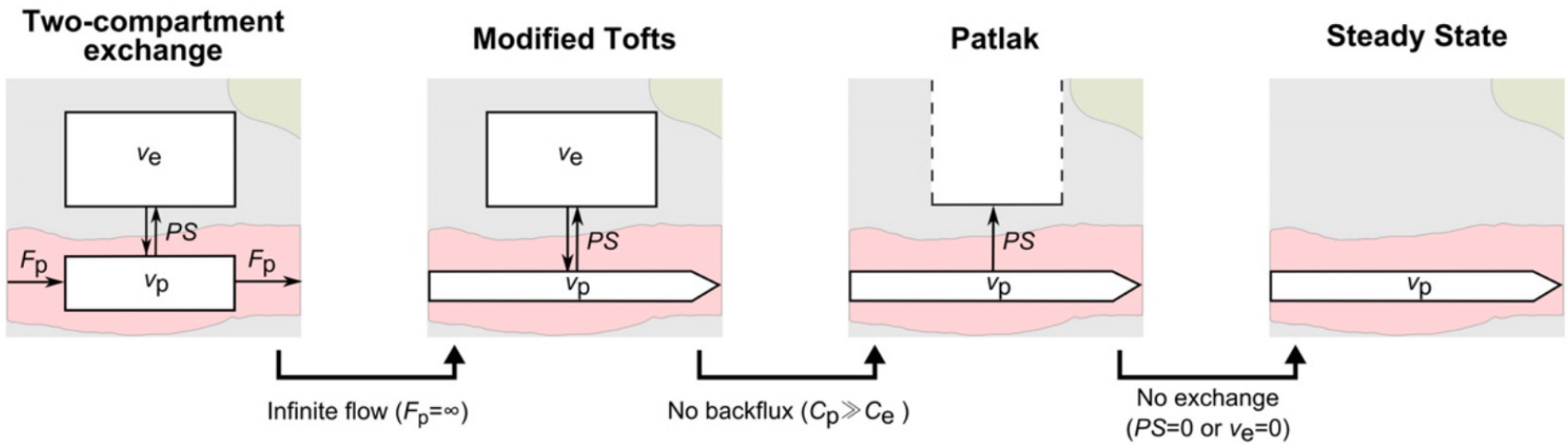

Fig. 2. Set of nested tracer kinetic models. Target parameters of DCE-MRI modelling are the fractional plasma volume v_p, the fractional interstitial volume v_e, the plasma flow F_p and the permeability-surface area product *PS*. The four models are related by a series of simplifying assumptions.