Coronary microvascular dysfunction is associated with impaired cognitive function: the Cerebral-Coronary Connection study (C3 study)

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Abstract

Background	It remains unknown whether the presence of coronary microcirculatory dysfunction (CMD) correlates with its equivalent condition in the brain, cerebral small vessel disease (CSVD). The cerebral-coronary connection (C3), a prospective blinded study, investigated the prevalence of CMD in patients with coronary artery disease (CAD) and its association with CSVD and cognitive function.
Methods and results	Patients with documented CAD fulfilling inclusion criteria underwent physiological assessment of epicardial vessels and the microcirculation using intracoronary pressure and Doppler. Coronary microcirculation-related indices included coronary flow reserve (CFR) and hyperaemic microvascular resistance. Brain magnetic resonance imaging, transcranial Doppler (TCD), and neurocognitive examination were performed. Overall, 67 patients were included in the study (mean age 66 years, 73% female). Patients with abnormal CFR (<2.0) (55.2%) showed higher burden of white-matter hyperintensities: 43.2 vs. 20.0% ($P = 0.044$). After statistical adjustment, low CFR was associated with lower grey matter volume ($P = 0.024$) and with parameters of white-matter microstructural damage in diffusion-tensor imaging (lower fractional anisotropy and higher mean diffusivity, $P = 0.029$ and $P = 0.032$, respectively). Low CFR was associated with higher resistive ($P = 0.027$) and pulsatility ($P = 0.043$) values on TCD, and worse neurocognitive test scores (lower mini mental state examination, $P = 0.025$, and slower Trail Making Test A, $P = 0.034$).
Conclusions	Coronary microcirculatory dysfunction is frequent in patients with CAD and correlates with CSVD, abnormal cerebral flow haemodynamics, and significant cognitive impairment. These findings support the hypothesis that microvascular dysfunction in the heart and the brain are part of a single pathological process affecting microcirculation in patients with CAD.
Clinical Trial Registration	ClinicalTrials.gov NCT04131075.

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Structured Graphical Abstract

Key Question
Is coronary microvascular dysfunction (CMD) associated with cerebral small vessel disease (CSVD)?

Key Finding
Patients with CMD showed imaging markers of CSVD in brain MRI, worse neurocognitive performance and disturbed cerebral flow in transcranial Doppler examinations.

Take Home Message
In patients with IHD, CMD was associated with CSVD and cognitive impairment, suggesting that both entities may be part of a wider systemic disorder.
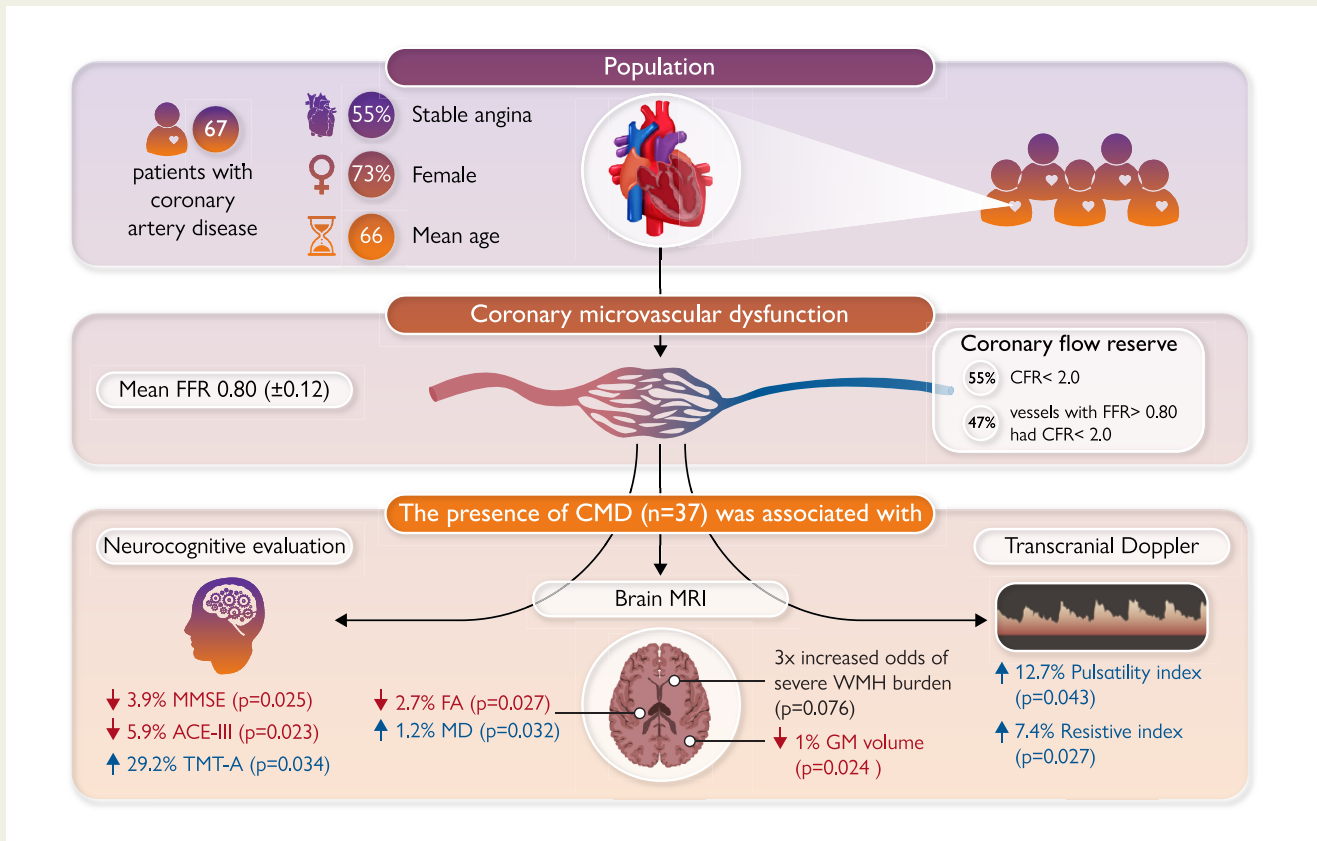
CFR, coronary flow reserve; FFR, fractional flow reserve; MMSE, mini mental state examination; ACE-III, Addenbrooke's Cognitive Examination (attention domain); TMT-A, Trail Making Test A; MRI, magnetic resonance imaging; WMH, white-matter hyperintensity; FA, fractional anisotropy; MD, mean diffusivity; GM, grey matter.

Keywords   Ischaemic heart disease • Coronary microvascular dysfunction • Cerebral small vessel disease • Cognitive impairment

Introduction

Ischaemic heart disease (IHD) and degenerative brain disease are two major sources of death and disability affecting all countries.[1] While the consequences of obstructive disease in major vessels supplying blood to both organs have been widely documented, less attention has been paid to disease processes affecting the microcirculation that, ultimately, may affect cardiac and cerebral function. Yet, over the last decade significant progress has been made in understanding the substrate of microvascular disease in both organs. In the heart, arteriolar thickening and capillary rarefaction that reduce the conductance of the microvasculature and its ability to vasodilate in response to increased myocardial oxygen demands constitute the leading cause of coronary microvascular dysfunction (CMD).[2] In the brain, concentric hyaline thickening of deep penetrating small arteries (arteriolosclerosis) with associated fibrosis of the vessel wall constitutes the most frequent substrate for cerebral small vessel disease (CSVD). Of note, both CMD and CSVD share common risk factors, such as age, hypertension, and diabetes.[3] These factors might have a common effect on the microvascular domain of cardiac and cerebral vascular beds.

Although a potential link between both conditions has been hypothesized[4] based on the similarities between pathological changes and risk factors, advance in knowledge exploring this has been hampered by lacking objective evidence of CMD and pathological brain changes indicative of CSVD in prior research studies. Thus, the relationship between CMD and CSVD is unknown.

The main objective of this study was to analyse the relationship between cerebrovascular disease and CMD in patients with atherosclerotic coronary artery disease (CAD).

Methods

Study design and protocol

The cerebral-coronary connection (C3) study (NCT04131075) is a prospective, observational, and investigator-initiated study enrolling patients with IHD presenting either as chronic coronary syndromes (CCS) or acute coronary syndromes (ACS) after stabilization. Patients with angiographically intermediate coronary stenoses suitable to fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) with drug-eluting stents were considered candidates for enrolment. In case of ACS as clinical presentation, only non-infarct-related arteries were evaluated at a staged procedure. Inclusion and exclusion criteria are shown in Supplementary material online, Table S1. This study was funded by Instituto Carlos III (Madrid, Spain) and co-financed by FEDER (Fondo Europeo de Desarrollo Regional) under the framework 'Proyectos Integrados de Excelencia' (PIE16/00043).

The complete study protocol is available in ClinicalTrials.gov (identifier NCT04131075). Following the patient's acceptance and the sign of informed consent, cardiac catheterization with intracoronary physiological evaluation was performed. Then, patients underwent several tests, including comprehensive neurocognitive assessment, transcranial Doppler (TCD) examination, and brain magnetic resonance (BMR). Investigators involved in these evaluations were blinded with respect to the initial results of the coronary microcirculation assessment. Local ethics committee approved the study protocol (C.I. 16/563-E).

Invasive assessment of the coronary microcirculation

Intracoronary physiological assessment was performed using a guiding catheter (5–7 Fr) and a dual pressure-Doppler sensor-tipped wire (ComboWire, Volcano, San Diego, CA, USA). After intracoronary nitrate administration (200 µg) and pressure equalization, the physiology wire was positioned distally to any existing stenosis. Mean aortic pressure, mean intracoronary distal pressure, Pd/Pa, and average peak flow velocity (APV) were registered at baseline conditions. Measurements were repeated under myocardial hyperaemia induced with intravenous adenosine (140 µg/kg/min). At the end of these measurements, a wire pullback was performed to rule out pressure drift. Fractional flow reserve was defined as the lowest Pd/Pa ratio under maximal stable hyperaemia, coronary flow reserve (CFR) as the ratio of hyperaemic APV to baseline APV, and hyperaemic microvascular resistance (HMR) as the ratio of hyperaemic distal pressure to hyperaemic APV. Whenever needed, correction of the envelope of spectral Doppler signal was performed using a dedicated programme coded with R (R Foundation for Statistical Computing, Vienna, Austria).

An FFR ≤ 0.80 was used to decide whether PCI was indicated, although performance of revascularization was left to operator discretion.[5] Percutaneous coronary intervention was performed using last-generation drug-eluting stents. For coronary lesions with FFR >0.80, PCI was deferred, and medical treatment was optimized.

Brain magnetic resonance and characterization of cerebral tissue damage

Brain magnetic resonance was acquired in a 1.5 T GE HDxt magnet, using an eight-channel high resolution receive coil. The protocol included the following series: axial 3D fast spoiled gradient-echo inversion recovery prepped T1-weighted sequence, a sagittal 3D fluid-attenuated inversion recovery sequence, an axial 3D susceptibility-weighted (SWI) sequence, and an axial diffusion-tensor imaging (DTI) echo-planar spin-echo sequence. The technical information for the acquisition of these sequences is detailed in Supplementary material online, Table S2.

Analysis of BMR images was performed as follows: first, visual assessment of small vessel disease using the 3D FLAIR sequence was performed qualitatively. Then, white-matter hyperintensities (WMHs) were manually segmented, generating a lesion map for each individual, and a quantitative measure of volume (in mm^3) (Supplementary material online, Figure S1). Semi-quantitative determination of number and location of microhaemorrhages were performed over the SWI sequence. The 3D FSPGR T1 was processed with the FAST, FIRST, and SIENAX tools of the FSL 6.0 toolbox (Functional Magnetic Resonance Imaging of the Brain Analysis Group, Oxford, UK), obtaining measures of intracranial volume, global brain volume, brain parenchymal fraction (BPF), grey matter volume, and white-matter volume, in cubic millimetres (mm^3). Normalization of the volumes for each individual was performed using the scaling factor needed for the register with the MNI 152 standard brain. The 3D FLAIR sequence was registered to the 3D FSPGR in order to use the T2 lesion map for generating a normal appearing white-matter mask (after the exclusion of the lesion areas), in addition to the initial white-matter mask. The DTI sequence was processed with the FDT pipeline of the FSL toolbox, first correcting eddy current distortions and then generating fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps after local fitting of diffusion tensors. The DTI sequence was registered to the 3D T1 sequence and cerebral white matter and normal-appearance cerebral white-matter global average values were then extracted from masked areas of the four diffusion derived maps.

Voxelwise statistical analysis of the DTI data was carried out using tract-based spatial statistics[6] that is part of FSL.[7] First, images were created using the nonlinear registration tool FNRIT, which uses a b-spline representation of the registration warp field.[8] Next, the mean imagen was created and thinned to derive a mean skeleton, which represents the centres of all tracts common to the group. Each subject's aligned value (FA, MD, AD, and RD) was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. For the creation of DTI images, areas of significant ($P < 0.05$ corrected for multiple comparisons) threshold-free cluster enhancement in patients with and without CMD were highlighted,[9] and represented over a standard skeleton (FMRIB58_FA), generating a visual representation of the areas with significant pathological values of FA, MD, RD, and AD.

Neurocognitive assessment and transcranial Doppler exams

Patients underwent neurocognitive assessment aimed to characterize the baseline cognitive function, and TCD to determine flow patterns of the cerebral circulation.

Neurocognitive assessment was done using a set of standardized instruments to assess the global cognition, attention and executive function, and episodic memory and verbal fluency (Supplementary material online, Table S3).

For TCD evaluation, the proximal segment (M1) of the middle cerebral artery was assessed utilizing a 2 MHz pulsed-wave probe through the transtemporal window. Flow velocities, Gosling's pulsatility index (PI), and Pourcellot's resistance index (RI) in the middle cerebral arteries were studied.

Data collection

All demographic data and baseline clinical characteristics, results of invasive coronary physiology assessment, imaging tests including BMR and TCD, and clinical neurocognitive assessment, were prospectively and confidentially

registered in a dedicated online electronic database according to national legislation and keeping the blinding between researchers.

Statistical analysis

For descriptive statistics, the population was divided according to previously established cut-offs of CFR (2.0) and HMR (2.5).[10] Low CFR (<2.0) was set as the marker of CMD. For patients with more than one vessel evaluated in the index procedure, either the lowest CFR or the highest HMR values were selected. The comparison of patients with and without CMD was done using the χ^2 or Fisher's exact tests for categorical variables, and with Student's *t*-test or Wilcoxon's signed-rank test for continuous variables.

For a categorical assessment of WMH, lesion volume measured in T2 sequences was divided in three tercile groups: low (lower third of the variable distribution, <570 mm^3), intermediate (between lower and upper third), and high (upper third, >2000 mm^3).

For the analysis of BMR, neurocognitive evaluation and TCD data, mean (or median when appropriate) values were compared in patients with and without CMD. Adjustment for age was also performed to account for a potential bias in neurocognitive scores. Then, the relation between CFR, BMR, and TCD variables as continuous variables was done first in an unadjusted manner using Spearman's ρ correlation coefficient. Then, linear regression was used to adjust for pre-specified baseline variables (age, gender, hypertension, and diabetes mellitus), deriving beta coefficients with 95% confidence intervals (CI).

To account for the influence of upstream epicardial stenosis on the underlying values of CFR or HMR, we also performed an additional analysis in two ways: (i) adding FFR as a continuous variable to the given linear model, or (ii) using the subgroup of patients with FFR >0.80.

As an additional calculation, a predictive logistic regression model for the detection of high burden of WMH was developed. Initial candidate variables were the presence of CMD (CFR <2.0), age, gender, hypertension, diabetes, dyslipidaemia, body mass index, tobacco use, and low FFR (≤0.80). We compute all the possible models and the final one was selected based on the lowest Akaike's Information Criterion (AIC).[11,12] The given logistic model was used to derive odds ratio (OR) with 95% CI for the occurrence of high burden of WMH.

For the linear models, normality and homoscedasticity were tested via the analysis of residuals, showing no major violations of these principles, except for WMH volume. In this particular case, logarithmic transformation of WMH (log-WMH) was performed and a log-linear model was used, demonstrating adequate fitting.

All analyses were carried out using STATA software, version 14 (StataCorp, College Station, TX, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Study population

From April, 2017 to February, 2020, a total of 85 patients were initially screened (*Figure 1*). Of them, 82 underwent intracoronary physiological evaluation. Brain magnetic resonance and neurocognitive evaluation were achieved in 67 patients, being this the final population deemed for analysis. Among them, TCD was performed in 57 patients. To assess for any potential selection bias, selected and unselected populations were compared according to their baseline clinical characteristics, showing no major differences (Supplementary material online, *Table S4*).

Clinical characteristics

Mean age was 66.0 years, and 49 patients were female (73.1%). Cardiovascular risk factors, baseline comorbidities, and treatment are depicted in *Table 1*. The main indication for coronary angiography was stable angina (55.2%). One quarter of the patients had previous myocardial infarction (25.4%), and nearly half of them had previous PCI (46.3%). After 1 year of follow-up, none of the patients had any clinical event (death, myocardial infarction, new revascularization, new admission due to cardiovascular causes, or stroke).

Intracoronary physiological evaluation

Angiographic and intracoronary physiological measurements are shown in *Table 2*. The left anterior descending coronary artery was the coronary vessel most frequently assessed (59.7% of patients). Coronary stenoses were intermediate according to angiography and functional evaluation (% of diameter stenosis 55.8 ± 12.6 and FFR 0.80 ± 0.12).

Mean CFR was 1.94. Thirty-seven patients (55.2%) had low CFR (<2.0), while 30 had preserved CFR (CFR ≥2.0, 44.8%). Mean FFR of the overall population was 0.80 (0.82 in those with CFR ≥2.0 and 0.79 if CFR <2.0, *P* = 0.259). Mean HMR was 2.7, being higher in patients with low CFR (3.0 vs. 2.3, *P* = 0.012). Percutaneous coronary intervention was performed in 29.9% of the evaluated vessels.

Brain magnetic resonance
Cerebral volumes and white-matter hyperintensities

Tables 3 and *4* show the relevant findings of BMR evaluation in this population. Binary analysis showed that patients with CMD had a 0.94% lower GM volume, while total brain tissue and white-matter volumes remained relatively constant. A positive relation between CFR and GM volume, which was independent of age, gender, hypertension, and diabetes (adjusted beta 11.33, *P* = 0.027), was documented. From this model we can estimate that, for each 0.1 reduction in CFR, GM volume decreases by 1.1 cm^3. No significant relations were observed between CFR and total brain tissue volume or BPF. A slight negative trend could be seen with white-matter volume, although small in magnitude (beta −8.95, *P* = 0.168, Supplementary material online, *Figure S3*).

Overall, WMH volume found in this cohort was low (median 1070 mm^3, 0.20% of the whole WM volume). In patients with CFR ≥2.0, median WMH volume was 1029.5 mm^3, whereas in those with CMD was 1515 mm^3. Noteworthy, patients with CMD had an increased prevalence of higher burden of WMH (43.2 vs. 20.0%, *P* = 0.044). The logistic regression analysis showed that, from a wide range of baseline variables, the best predictive model for the detection of high burden of WMH (>2000 mm^3) according to AIC was constituted by age, hypertension, and the presence of CMD (model's AIC 76.2 and AUC 0.791) (*Figure 2*).

Although not reaching statistical significance, the adjusted lineal model showed a remarkable negative relation between WMH volume as a continuous variable and CFR (beta −0.20, *P* = 0.469). This trend can also be noted when compared aggregated images of WMH in patients with and without CMD (*Figure 3*).

Diffusion-tensor imaging-derived parameters

Diffusion-tensor imaging analysis of the normal-appearance white matter showed that patients with CMD presented lower FA, as well as higher MD and RD (Supplementary material online, *Figure S2*).

After adjustment for baseline covariates, CFR as a continuous variable demonstrated a positive relation with FA (beta 6.31×10^{-3}, *P* = 0.027), and a negative relationship with MD and RD (beta -8.27×10^{-6}, *P* = 0.032 and beta -9.73×10^{-6}, *P* = 0.029, respectively). These relations were also present, although slightly less pronounced, after adjustment for FFR (*Table 4*).
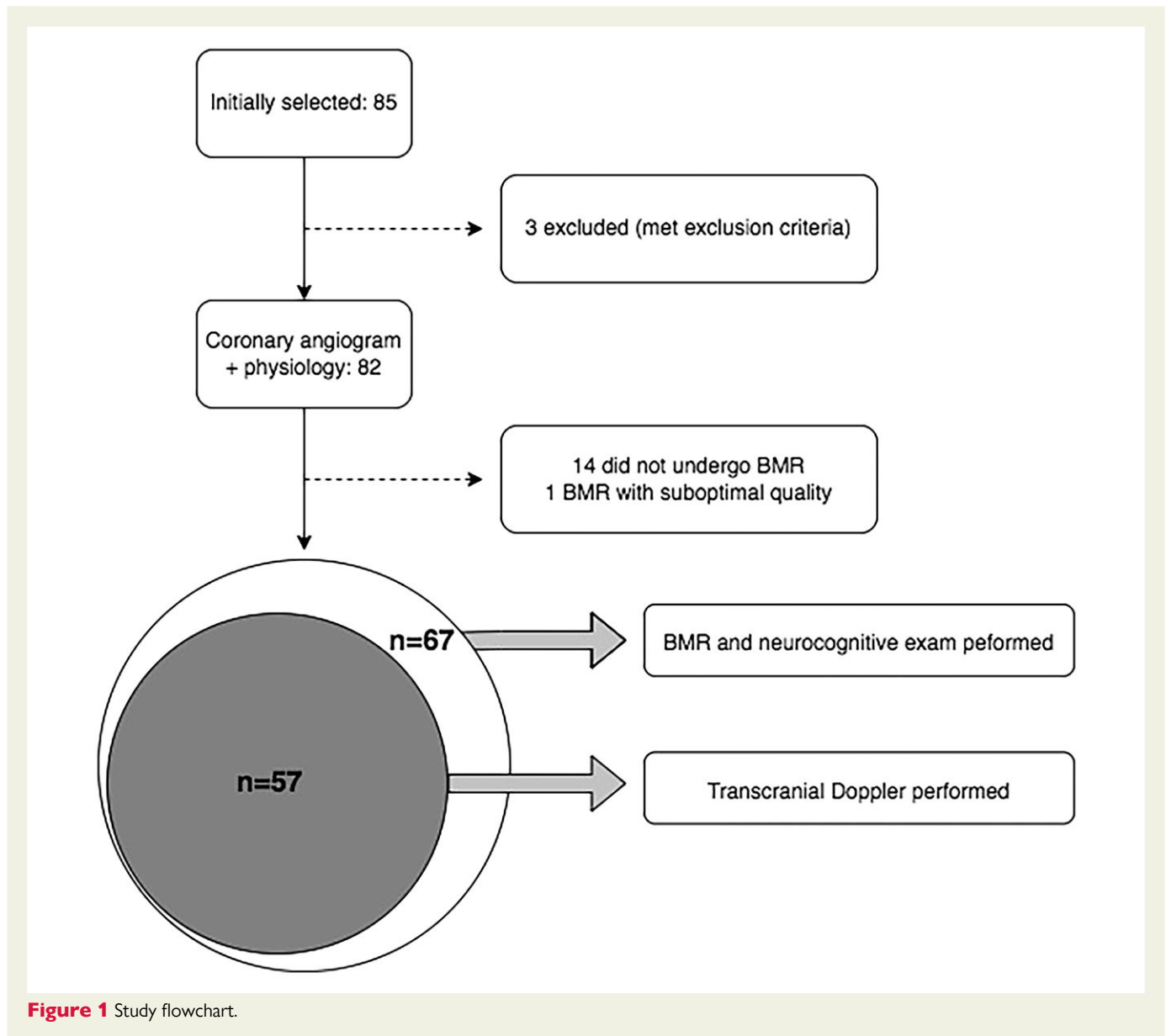
Figure 1 Study flowchart.

Voxelwise representation of DTI-derived data revealed that the differences observed in patients with CMD were more pronounced in frontal and temporal white matter. In addition, patients with CMD showed lower FA and higher RD in the genu of the corpus callosum, the external capsule, and the anterior limb of the internal capsule of both hemispheres. Mean diffusivity was also higher in those areas but restricted to the right hemisphere (*Figure 4*).

Finally, HMR did not show significant associations with brain volumes or DTI-derived parameters. Only a weak positive relation was found with MD (ρ 0.239, $P = 0.048$), AD (ρ 0.252, $P = 0.037$), and RD (ρ 0.232, $P = 0.056$) that was significantly dwindled after adjustment for baseline cardiovascular risk factors (Supplementary material online, *Table S5*).

Neurocognitive assessment and transcranial Doppler

Then main results of these evaluations are presented in *Tables 5 and 6*, respectively.

The assessment with quantitative scales showed that patients with CMD presented lower scores in mini mental state examination (27.4 vs. 28.5, $P = 0.025$), Addenbrooke's Cognitive Examination III (ACE-III, attention domain: 16.0 vs. 17.0, $P = 0.023$), and slower score in Trail Making Test-A (TMT-A, 62.8 vs. 48.6, $P = 0.034$).

In TCD exams, median PI and RI were significantly higher in patients with CMD: 1.14 vs. 1.02, $P = 0.032$ for PI and 0.65 vs. 0.61, $P = 0.022$ for RI. Adjusted analysis showed that both indices had a significant negative relation with CFR (beta -0.06 for PI, $P = 0.043$; beta -0.02 for RI, $P = 0.027$), as depicted in *Figure 5*. Hyperaemic microvascular resistance did not show any significant relationship with either clinical neurocognitive evaluation or TCD in this population.

Discussion

In this prospective study, we found that the presence of CMD in patients with CAD is linked to microvascular-related changes in the brain as revealed by BMR and TCD, including higher prevalence of WMH,

Table 1 Baseline characteristics of the population

Variable	All (n = 67)	CFR ≥2.0 (n = 30)	CFR <2.0 (n = 37)	P-value
Clinical characteristics				
Age	66.0 (±8.8)	65.0 (±8.6)	66.9 (±9.0)	0.378
Female sex	49 (73.1)	23 (76.7)	26 (70.3)	0.557
Hypertension	42 (62.7)	18 (60.0)	24 (64.9)	0.682
Dyslipidaemia	43 (64.2)	18 (60.0)	25 (67.6)	0.521
Diabetes	21 (31.3)	10 (33.3)	11 (29.7)	0.752
On insulin	8 (11.9)	4 (13.3)	4 (10.8)	0.752
Smoking				0.916
Never	28 (41.8)	12 (40.0)	16 (43.2)	
Former	27 (40.3)	12 (40.0)	15 (40.5)	
Active	12 (17.9)	6 (20.0)	6 (16.2)	
Family history of CAD	8 (11.9)	4 (13.3)	4 (10.8)	0.752
CKD	3 (4.5)	0 (0)	3 (8.1)	0.247
Previous MI	17 (25.4)	7 (23.3)	10 (27.0)	0.730
Previous cancer	6 (9.0)	1 (3.3)	5 (13.5)	0.213
Previous PCI	31 (46.3)	12 (40.0)	19 (51.4)	0.354
LVEF (%)	59.5 (±8.7)	60.1 (±6.9)	59.1 (±9.8)	0.754
Indication for angiography				0.728
SA	37 (55.2)	15 (50.0)	22 (59.5)	
ACS	22 (32.8)	11 (36.7)	11 (29.7)	
Other	8 (11.9)	4 (13.3)	4 (10.8)	
Medical treatment				
Aspirin	54 (80.6)	27 (90.0)	27 (73.0)	0.080
Clopidogrel	12 (17.9)	4 (13.3)	8 (21.6)	0.525
Ticagrelor	10 (14.9)	4 (13.3)	6 (16.2)	0.742
Prasugrel	4 (6.0)	3 (10.0)	1 (2.7)	0.318
Anticoagulants	1 (1.5)	0	1 (2.7)	1.000
ACEI	24 (35.8)	11 (36.7)	13 (35.1)	0.897
ARBs	11 (16.4)	3 (10.0)	8 (21.6)	0.321
Beta-blockers	31 (46.3)	17 (56.7)	14 (37.8)	0.124
CCBs	7 (10.5)	6 (20.0)	1 (2.7)	0.039
Nitrates	12 (17.9)	5 (16.7)	7 (18.9)	0.811
Statins	46 (68.7)	19 (63.3)	27 (73.0)	0.398

Results are shown as mean (±standard deviation) or n (%). CAD, coronary artery disease; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; SA, stable angina; ACS, acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

structural derangements in white brain matter structure, grey matter atrophy, and cerebral flow abnormalities. In addition, we found that CMD is associated with worse neurocognitive test scores, reflecting subclinical impairment of cognitive function (*Structured Graphical Abstract*).

A key question regarding CMD and CSVD is whether these conditions are organ-specific or, alternatively, part of a systemic disorder involving the microcirculation of other organs. In support of the latter hypothesis, prior studies have shown a relationship between microvascular abnormalities in the kidney and the retina with CMD and

Table 2 Angiographic characteristics and intracoronary physiological assessment

Variable	All (n = 67)	CFR ≥2.0 (n = 30, 44.8%)	CFR <2.0 (n = 37, 55.2%)	P-value
Angiographic characteristics				
No of vessels with CAD				
0	1 (1.5)	1 (3.3)	0 (0)	0.082
1	25 (37.3)	12 (40.0)	13 (35.1)	
2	25 (37.3)	7 (23.3)	18 (48.7)	
3	16 (23.9)	10 (33.3)	6 (16.2)	
Target vessel				
LAD	40 (59.7)	21 (70.0)	19 (51.4)	0.302
LCX	12 (17.9)	4 (13.3)	8 (21.6)	
RCA	15 (22.4)	5 (16.7)	10 (27.0)	
Diameter stenosis (%)	55.8 (±12.6)	55.4 (±13.9)	56.2 (±11.7)	0.816
Lesion length, mm	13.2 (±6.0)	13.8 (±5.4)	12.8 (±6.5)	0.581
PCI performed	20 (29.9)	8 (26.7)	12 (32.4)	0.608
Intracoronary physiological measurements				
CFR	1.94 (±0.80)	2.57 (±0.78)	1.43 (±0.32)	<0.001
Pd/Pa	0.91 (±0.14)	0.91 (±0.19)	0.92 (±0.09)	0.876
FFR	0.80 (±0.12)	0.82 (±0.09)	0.79 (±0.14)	0.259
>0.80	38 (56.7)	20 (66.7)	18 (48.7)	0.139
≤0.80	29 (43.3)	10 (33.3)	19 (51.4)	
HMR	2.7 (±1.3)	2.3 (±0.99)	3.0 (±1.4)	0.012
<2.5	32 (47.8)	18 (60.0)	14 (37.8)	0.071
≥2.5	35 (52.2)	12 (40.0)	23 (62.2)	
Basal APV	15.7 (±6.9)	13.3 (±5.3)	17.4 (±7.5)	0.021
Hyperaemic APV	27.9 (±11.4)	32.6 (±11.2)	24.6 (±10.5)	0.006

Results are shown as mean (±standard deviation) or n (%). CAD, coronary artery disease; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; CFR, coronary flow reserve; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; HMR, hyperaemic microvascular resistance; APV, average peak velocity.

CSVD,[13–15] as well as an association between CMD and endothelial function of the peripheral arteries.[16] Remarkably, the relationship between CMD and CSVD has not been investigated despite many similarities in the pathological processes involved in both conditions. Apart from phasic variations in the heart circulation associated with the cardiac cycle and the presence of the blood barrier in the brain, other major structural and functional characteristics of the microcirculation are shared by both organs. Arterioles regulate perfusion according to metabolic requirements of the myocardium and cerebral parenchyma, and pathological mechanisms of microvascular dysfunction, like thrombosis, atherosclerosis, capillary rarefaction, and arteriolar remodelling, have been described or proposed for the heart and the brain.[17] Furthermore, CAD shares vascular risk factors with stroke, cognitive decline, and other neurodegenerative disorders, and some rare genetic diseases targeting the microcirculation have shown to produce concomitant brain injury and CMD.[18] Based on all this, the main aim of the C3 study was to investigate the existence of such relationship in a prospective manner and using a solid methodological approach in the context of paucity of data. Of note, we

focused our research on patients who had evidence of coronary atherosclerosis, assuming that the coexistence with CMD represents the utmost expression of CAD.

Clinical relevance of coronary microcirculatory dysfunction in patients with ischemic heart disease

Objective documentation of CMD was a key aspect of our study. We used CFR as the index of choice for this purpose, given the extensive evidence supporting its prognostic predictive value.[19] According to CFR, we observed a prevalence of CMD higher than previous studies,[20,21] most likely related to the fact that our study cohort was predominantly constituted by women, who have shown a higher prevalence of CMD than males.[22] Identifying CMD is growingly acknowledged as a key step in setting stratified effective medical treatment in patients with symptomatic IHD.[23] Furthermore, as widely demonstrated, low CFR is an important

Table 3 Relation between coronary flow reserve (categorical variable) and brain magnetic resonance variables

Variable	All (n = 67)	CFR ≥2.0 (n = 30)	CFR <2.0 (n = 37)	P-value
Cerebral volumes				
Total brain volume (cm^3)	1412.4 (±106.6)	1405.1 (±94.3)	1412.4 (±109.0)	0.940
GM volume (cm^3)	821.9 (±75.6)	823.3 (±58.6)	815.6 (±77.4)	0.212
WM volume (cm^3)	581.3 (±42.5)	579.6 (±35.7)	585.8 (±47.8)	0.508
WMH volume (mm^3)	1070 (±4101)	1029.5 (±1703)	1515 (±5999)	0.413
Low (<570 mm^3)	23 (34.3)	10 (33.3)	13 (35.2)	0.877
Intermediate (570–2000 mm^3)	22 (32.8)	14 (46.7)	8 (21.6)	0.030
High (>2000 mm^3)	22 (32.8)	6 (20.0)	16 (43.2)	0.044
WMH volume (% of total WM)	0.20 (0.68)	0.18 (0.27)	0.24 (0.95)	0.461
BPF	0.730 (±0.027)	0.731 (±0.024)	0.728 (±0.027)	0.738
Microbleedings				
No	57 (85.3)	27 (90.0)	30 (81.6)	0.494
Yes	10 (14.7)	3 (10.0)	7 (18.92)	
Diffusion-tensor imaging measurements				
NAWM—FA	0.367 (±0.025)	0.371 (±0.022)	0.361 (±0.027)	0.032
NAWM—MD	0.81 (±0.03) × 10^{-3}	0.81 (±0.03) × 10^{-3}	0.82 (±0.03) × 10^{-3}	0.027
NAWM—AD	1.15 (±0.04) × 10^{-3}	01.14 (±0.04) × 10^{-3}	1.15 (±0.03) × 10^{-3}	0.182
NAWM—RD	0.64 (±0.04) × 10^{-3}	0.64 (±0.026) × 10^{-3}	0.66 (±0.041) × 10^{-3}	0.020
GM—MTR	0.349 (±0.039)	0.347 (±0.058)	0.349 (±0.037)	0.301
NAWM—MTR	0.423 (±0.044)	0.416 (±0.057)	0.428 (±0.037)	0.276

Results are shown as median (±interquartile range) or *n* (%). GM, grey matter; WM, white matter; WMH, white-matter hyperintensity; NAWM, normal-appearance white matter; BPF, brain parenchymal fraction; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; MTR, magnetization transfer ratio.

marker of cardiovascular risk at long-term follow-up across several clinical subsets.[19]

Based on pressure and coronary flow velocity, we also assessed HMR as an additional index of structural CMD. At a difference with CFR, no significant relationships were found between features of CSVD and HMR. This can be due to the fact that HMR has a lower predictive value than CFR in predicting patient outcomes.[19] However, despite the lack of association between HMR and brain tests in this study, we still think that microcirculatory resistance-derived indices are an important part of the comprehensive assessment of coronary microcirculation, and future studies will bring clarity about their real importance.

Relationship between microvascular impairment in the heart and the brain

As occurs with the coronary microcirculation, cerebral small vessels cannot be directly visualized *in vivo*. The clinical manifestations of CSVD are diverse: from stroke symptoms to vascular dementia or depression, or largely asymptomatic and only revealed by brain imaging.[24] Classic BMR imaging findings of CSVD include subcortical infarcts, WMH, cerebral microbleedings, enlarged perivascular spaces, and cerebral atrophy.[25] From a pathophysiological standpoint, ischaemia on the capillary beds causes loss of myelin and gliosis that can be detected on T2-weighted sequences as WMH. Ongoing ischaemic injury may produce, if persistent, subcortical infarcts. And finally, leakage of blood products out of microaneurysms result in microbleedings.[26] There is strong evidence that CSVD is associated with higher mortality, morbidity, and increased health care costs.[27]

We focused on identifying WMH and grey matter atrophy (hallmarks of CSVD), and both were found to be related with the presence of CMD. Patients with low CFR demonstrated significantly lower GM volume and higher burden of WMH, even though the total amount of macroscopic lesion in this population was low.

Classic BMR findings of CSVD refer to established and advanced forms of cerebral vascular disease. Novel techniques used in our study, such as DTI, provide *in vivo* assessment of WM microstructure.[28] Diffusion-tensor imaging examines the diffusion of water molecules, which is dependent on the presence of barriers in neural tissue. Within normal WM, axonal cell membranes and myelin sheaths restrict perpendicular movement of water, causing the primary direction of diffusion to run along the fibre bundle. Fractional anisotropy and MD are the most frequently used parameters derived from voxelwise DTI modelling. Low FA or high MD indicate a loss of directionality of water molecules, typically triggered by axonal degeneration and demyelination.[29] As these abnormalities herald the development of macroscopic lesions (WMH), they may be used to detect earlier stages of CSVD.

Table 4 Relation between coronary flow reserve and brain magnetic resonance variables

Variable	Unadjusted		Model 1: adjusted by age, gender, hypertension, and diabetes		Model 2: adjusted by age, gender, hypertension, diabetes, and FFR		Model 3: adjusted by age, gender, hypertension, and diabetes only when FFR >0.80	
	Spearman's ρ	P-value	Beta coefficient (95%CI)	P-value	Beta coefficient (95%CI)	P-value	Beta coefficient (95%CI)	P-value
Total brain volume (cm^3)	0.061	0.626	2.37 (−15.74 to 20.48)	0.794	5.97 (−13.20 to 25.04)	0.533	13.96 (−6.43 to 34.36)	0.173
GM volume (cm^3)	0.189	0.128	11.33 (1.52–21.14)	0.024	12.09 (1.66–22.53)	0.024	15.63 (3.17–28.09)	0.016
WM volume (cm^3)	−0.083	0.502	−8.95 (−21.79 to 3.88)	0.168	−6.12 (−6.12 to 7.36)	0.367	−1.66 (−12.39 to 9.07)	0.754
WMH volume (mm^3)[a]	−0.111	0.374	−0.20 (−0.72 to 0.31)	0.469	−0.28 (−0.83 to 0.28)	0.322	−0.35 (−0.91 to 0.22)	0.222
BPF	0.056	0.655	0.0023 (−0.003 to 0.007)	0.369	0.0019 (−0.004 to 0.007)	0.474	0.0037 (−0.003 to 0.101)	0.254
NAWM-FA	0.244	0.050	6.31 (0.76–11.9) $\times 10^{-3}$	0.027	5.54 (−0.26 to 11.3) $\times 10^{-3}$	0.061	5.07 (−0.57 to 10.7) $\times 10^{-3}$	0.076
NAWM-MD	−0.256	0.031	−8.27 (−15.8 to −0.75) $\times 10^{-6}$	0.032	−7.59 (−15.6 to 0.39) $\times 10^{-6}$	0.062	−6.86 (−14.9 to 0.12) $\times 10^{-6}$	0.094
NAWM-AD	−0.193	0.120	−5.38 (−12.1 to 1.36) $\times 10^{-6}$	0.116	−5.21 (−12.4 to 1.96) $\times 10^{-6}$	0.151	−4.88 (−12.7 to 2.95) $\times 10^{-6}$	0.214
NAWM-RD	−0.263	0.033	−9.73 (−18.4 to −1.03) $\times 10^{-6}$	0.029	−8.79 (−18.0 to 0.43) $\times 10^{-6}$	0.067	−7.91 (−17.1 to 1.23) $\times 10^{-6}$	0.087
NAWM-MTR	−0.153	0.233	−3.74 (−14.3 to 6.79) $\times 10^{-3}$	0.480	2.13 (−13.3 to 9.0) $\times 10^{-3}$	0.704	0.72 (−14.3 to 12.9) $\times 10^{-3}$	0.915

Results are shown as beta coefficient with 95% confidence interval (CI). CFR, coronary flow reserve; FFR, fractional flow reserve; GM, grey matter; WM, white matter; NAWM, normal-appearance white matter; BPF, brain parenchymal fraction; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; MTR, magnetization transfer ratio.
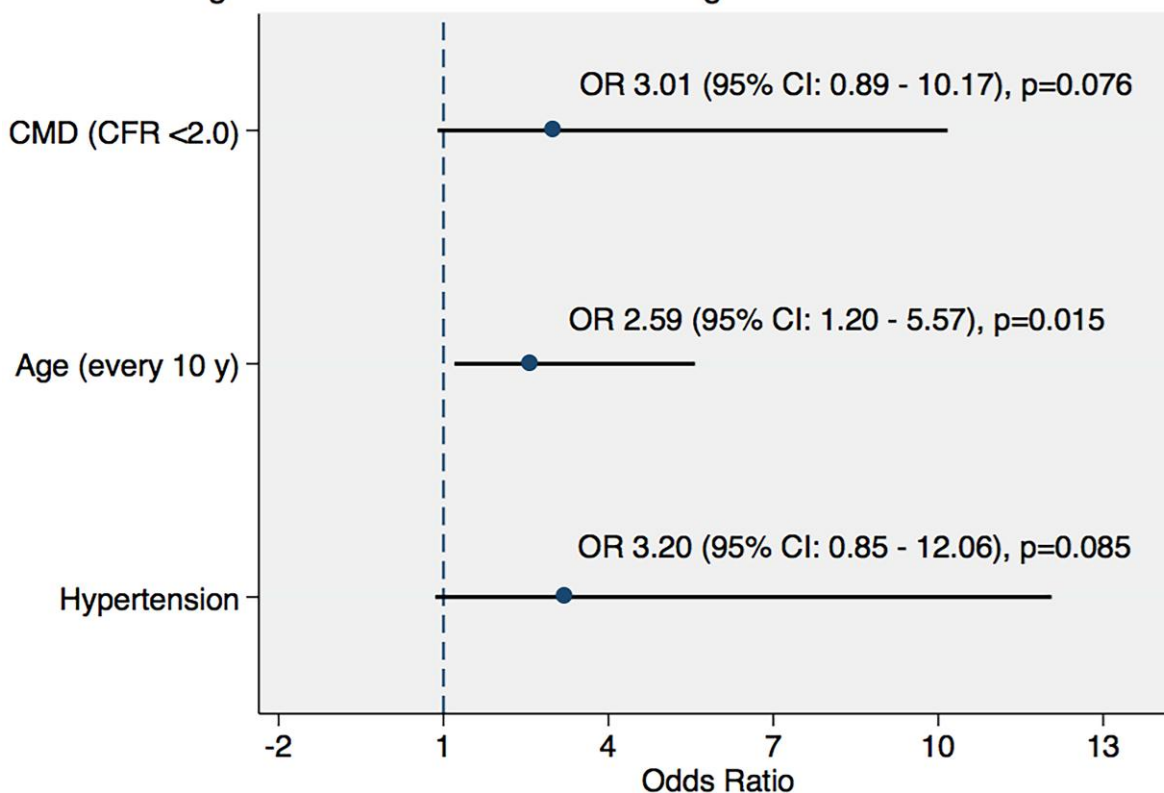[a]Log-linear model was used for WMH analysis.

Figure 2 Results of the final logistic model used for the prediction of high burden of white-matter hyperintensity. OR, odds ratio; CI, confidence interval; CMD, coronary microcirculatory dysfunction.
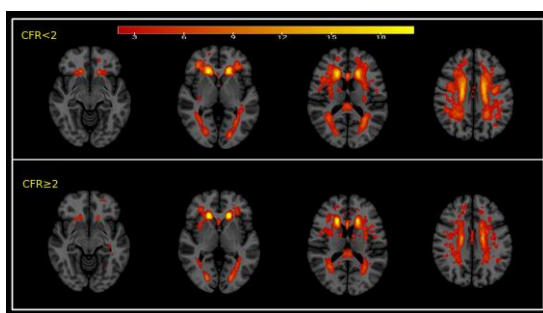

Figure 3 Aggregated representation of segmented T2-hyperintense areas after spatial normalization to a standard atlas (MNI152). Coloured areas denote presence of abnormal (hyperintense) white matter in 3D fluid-attenuated inversion recovery sequences. As can be estimated visually, abnormal white matter was more extensive in patients with coronary microcirculatory dysfunction (above) than in those without coronary microcirculatory dysfunction (below).
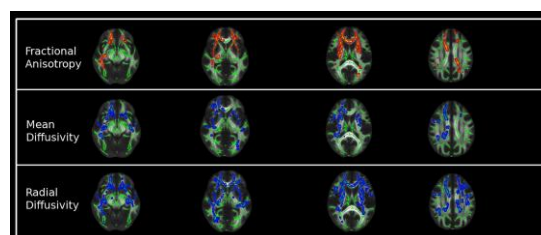

Figure 4 Tract-based spatial statistics voxelwise analysis of diffusion-tensor imaging-derived maps. The images show brain regions with significantly abnormal values of fractional anisotropy, mean, and radial diffusivity in patients with low coronary flow reserve. Patients with coronary microcirculatory dysfunction showed predominant abnormalities of fractional anisotropy and radial diffusivity in the genu of the corpus callosum, the external capsule, and the anterior limb of the internal capsule of both hemispheres. Abnormal mean diffusivity values were also seen in those areas but restricted to the right hemisphere.

In our study, the above-described imaging indices were useful in exploring the relationship between CMD and CSVD. Patients with CMD showed lower FA and higher MD, in concordance with the macroscopic BMR parameters. Coronary microcirculatory dysfunction was independently associated with CSVD, and not influenced by age, nor other cardiovascular risk factors or epicardial CAD as measured by FFR. Adjustment to patient age was of particular relevance, as ageing is strongly associated with structural brain disarrangements[3] and is also a key determinant of the vasodilator response in the heart.[30]

Table 5 **Relation of coronary flow reserve with neurocognitive clinical evaluation**

Variable	All ($n = 67$)	CFR ≥2.0 ($n = 30$)	CFR <2.0 ($n = 37$)	P-value	Age-adjusted P-value
Semi-quantitative scales					
MMSE (max. 30)	27.9 (±2.03)	28.5 (±1.8)	27.4 (±2.1)	0.025	0.041
ACE-III (global) (max. 100)	85.1 (±10.1)	87.0 (±8.2)	83.6 (±11.3)	0.184	0.242
ACE-III (attention) (max. 18)	16.5 (±1.8)	17.0 (±1.2)	16.0 (±2.0)	0.023	0.032
Digit span forward	5.3 (±0.89)	5.37 (±0.89)	5.33 (±0.89)	0.880	0.939
Digit span backwards	3.8 (±0.85)	3.8 (±0.85)	3.8 (±0.87)	1.000	0.872
TMT-A	56.2 (±27.1)	48.6 (±18.3)	62.8 (±31.7)	0.034	0.055
TMT-B	121.6 (±56.7)	107.2 (±36.3)	133.7 (±67.6)	0.073	0.113
TMT-B/TMT-A	2.37 (±0.62)	2.39 (±0.63)	2.35 (±0.61)	0.792	0.781
SDMT	31.2 (±12.2)	32.5 (±11.3)	30.1 (±13.0)	0.426	0.732
Interference (Stroop Colour Word Interference Test)	−3.03 (±7.9)	−1.83 (±8.7)	−4.01 (±7.3)	0.286	0.251
ToL (correct movements) (max. 10)	3.87 (±1.8)	4.04 (±1.9)	3.74 (±1.72)	0.521	0.535
ToL (total movements)	33.4 (±18.0)	31.4 (±15.5)	35.1 (±19.8)	0.424	0.442
Semantic verbal fluency (animals)	16.8 (±4.5)	16.3 (±3.8)	17.3 (±5.0)	0.398	0.231
FCRST—total recall (max. 48)	39.4 (±8.4)	40.7 (±6.5)	38.3 (±9.6)	0.253	0.336
FCRST—total delayed recall (max. 16)	13.2 (±3.2)	13.7 (±2.8)	12.9 (±3.5)	0.284	0.396

Results are shown as mean (±standard deviation). MMSE, mini mental state examination; ACE-III, Addenbrooke's Cognitive Examination III; TMT, Trail Making Test; SDMT, symbol digit modalities test; ToL, Tower of London; FCRST, free and cued selective reminding test. Interference of Stroop is calculated as Stroop C − [(A × B)/(A + B)] (A, word reading; B, colour naming; C, interference between word and colour).

Table 6 **Transcranial Doppler examination**

Variable	Unadjusted		Model 1: adjusted by age, hypertension, and diabetes		Model 2: adjusted by age, hypertension, and diabetes if FFR >0.80	
	Spearman's ρ	P-value	Beta coefficient (95% CI)	P-value	Beta coefficient (95% CI)	P-value
Right cranial artery mean velocity	−0.030	0.824	−0.84 (−4.1 to 2.4)	0.609	−0.35 (−4.60 to 3.89)	0.865
Left cranial artery mean velocity	−0.050	0.713	−1.55 (−4.6 to 1.5)	0.316	−1.61 (−5.00 to 1.78)	0.339
Pulsatility index	−0.285	0.032	−0.06 (−0.11 to 0.0)	0.043	−0.05 (−0.10 to 0.0)	0.067
Resistive index	−0.297	0.025	−0.02 (−0.04 to 0.0)	0.027	−0.02 (−0.03 to 0.0)	0.042

Results are shown as Spearman's ρ correlation coefficient (unadjusted) and adjusted linear regression beta coefficients with 95% confidence interval (CI). FFR, fractional flow reserve.

Assessment of cognitive function and its relationship with coronary microcirculatory dysfunction

In our study population, despite the absence of previously documented neurological disease or cognitive impairment, patients with CMD showed and age-independent worse performance in neurocognitive scores. The comprehensive evaluation using standardized scales highlighted some degree of attention and executive dysfunction, mirroring structural derangements noted in BMR, and suggesting cognitive consequences of brain damage, even in cognitively asymptomatic patients. A potential explanation for this association can be found in the microcirculation of the brain: previous studies have reported that cognitive impairment and executive functioning issues resulting from WM derangements are a frequent presentation of CSVD.[31] In this regard, cognitive impairment in presence of low CFR supports concomitant microcirculatory dysfunction in the heart and the brain.
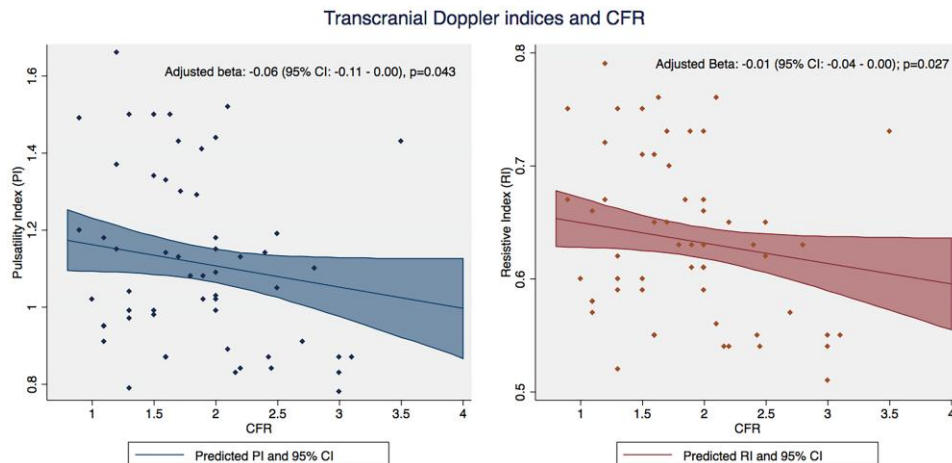
Figure 5 Relation between transcranial Doppler indices and coronary flow reserve. PI, pulsatility index (Gosling's index); RI, resistive index (Pourcelot's index).

Cerebral blood flow and coronary microcirculatory dysfunction

Normal arterial flow has a characteristic pulsatility. Under normal physiological conditions, the phasic increase in volume of blood entering the intracranial cavity is compensated by the outflow of cerebrospinal fluid and venous outflow from the cranial cavity. For the correct performance of this mechanism, integrity of the whole intracranial vascular system is warranted. Impaired vascular elasticity reduces arterial diameter, leading to higher flow resistance and higher blood pulsatility. These cerebral flow characteristics can be non-invasively measured by TCD examination, from which PI and RI can be derived. Distortions in cerebral blood flow, as assessed by TCD, have been associated with cognitive impairment[32] and with imaging findings of CSVD.[33] Abnormal PI and RI values, which most likely reflect downstream microcirculatory brain disease, were consistent with imaging and clinical data and occurred more frequently in patients with CMD.

Study strengths and limitations

To the best of our knowledge, this is the first prospective study specifically evaluating the relation of coronary and CSVD. In order to improve the quality of the evidence gathered, and avoid potential biases, our study was blinded at different levels: cardiology investigators were blinded with respect to BMR, neurocognitive evaluation and TCD. At vice versa, neurology and radiology investigators were blinded with respect to cardiology investigations; furthermore, patients were also blinded to coronary and cerebral microvascular assessment.

The present study is not free from limitations: first, it is a single-centre, observational study. Second, sample size was relatively small and there was a significant loss of patients due to the impact of the COVID-19 pandemic on the health systems during 2020 and 2021. Notwithstanding that, the blinded and prospective nature of this study, the comprehensive heart and neurological evaluation, and the objective assessment with several diagnostic techniques strongly support our results. Third, the population of this study represents patients with established atherosclerotic CAD, thus, these findings cannot be completely extrapolated to patients with ischaemia and no obstructive CAD. Fourth, we did not perform coronary spasm provocation tests, so

information regarding the relation of CSVD coronary vasomotor disorders is also lacking. Moreover, a great number of the catheterization laboratories use thermodilution-derived indices, including the index of microvascular resistance that although similar to HMR, is not completely equivalent. Fifth, despite all the analyses strongly indicate an association between CMD and CSVD, the issue of multiple statistical testing has to be taken into consideration, and the risk of a Type I error cannot be fully excluded. Finally, the results of this study should be considered as hypothesis-generating rather than conclusive.

Clinical implications

Ischaemic heart disease and degenerative brain diseases are, along with cancer, the most feared health threats in developed countries. The disclosure of a relationship between CMD and brain abnormalities attributable to CSVD emphasizes the critical importance of the microcirculation as a seat for disease in both organs. Any progress in consolidating knowledge in this field may, ultimately, result in the development of successful prevention and therapeutic policies that will ameliorate the heavy toll imposed by these serious conditions to the individual and the society.

Conclusions

In patients with atherosclerotic CAD, the presence of CMD, as determined by low CFR, is associated with CSVD, abnormal cerebral flow haemodynamics, and subtle but significant impairment of cognitive function. These findings support the hypothesis that microvascular dysfunction in the heart and the brain are part of a single pathological process in patients with coronary atherosclerosis.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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