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Mean arterial pressure change associated with cerebral blood flow in healthy older adults

Jeremy Deverdun [a,b,c,d,*], Tasnime N. Akbaraly [e,f,g,h,i], Celine Charroud [c,j], Meriem Abdennour [j,k], Adam M. Brickman [l], Stephane Chemouny [b], Jason Steffener [l], Florence Portet [j,k,m], Alain Bonafe [c], Yaakov Stern [l], Karen Ritchie [j,k,n], François Molino [a,c,d], Emmanuelle Le Bars [c], Nicolas Menjot de Champfleur [c,o]

[a] Laboratoire Charles Coulomb, CNRS UMR 5221, Université Montpellier II, Montpellier, France
[b] Intrasense, Montpellier, Hérault, France
[c] Department of Neuroradiology, Institut d'Imagerie Fonctionnelle Humaine, I2FH, University Hospital Center, Gui de Chauliac Hospital, Montpellier, France
[d] Institut de Génomique Fonctionnelle, UMR 5203, INSERM U661, Université Montpellier II, Université Montpellier I, France
[e] Inserm U 1198, Montpellier, France
[f] University Montpellier, Montpellier, France
[g] EPHE, Paris, France
[h] Department of Epidemiology and Public Health, University College London, London, UK
[i] Inserm U 710, Montpellier, France
[j] Inserm U 1061, Montpellier, France
[k] Université Montpellier I, Montpellier, France
[l] Cognitive Neuroscience Division, Department of Neurology, Columbia University, New York, USA
[m] Montpellier University Hospital, University Department of Adult Psychiatry, La Colombière Hospital, Montpellier, France
[n] Faculty of Medicine, Imperial College, London, England
[o] Team "Plasticity of Central Nervous System, Stem Cells and Glial Tumors", U1051, Institut of Neurosciences of Montpellier, Saint Eloi Hospital, Montpellier, France

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ABSTRACT

We investigate over a 12-year period the association between regional cerebral blood flow (CBF) and cardiovascular risk factors in a prospective cohort of healthy older adults (81.96 ± 3.82 year-old) from the Cognitive REServe and Clinical ENDOphenotype (CRESCENDO) study. Cardiovascular risk factors were measured over 12 years, and gray matter CBF was measured at the end of the study from high-resolution magnetic resonance imaging using arterial spin labeling. The association between cardiovascular risk factors, their long-term change, and CBF was assessed using multivariate linear regression models. Women were observed to have higher CBF than men ($p < 0.05$). Increased mean arterial pressure (MAP) over the 12-year period was correlated with a low cerebral blood flow ($p < 0.05$, $R^2 = 0.21$), whereas no association was detected between CBF and MAP at the time of imaging. High levels of glycemia tended to be associated with low cerebral blood flow values ($p < 0.05$). Age, alcohol consumption, smoking status, body mass index, history of cardiovascular disease, and hypertension were not associated with CBF. Our main result suggests that change in MAP is the most significant predictor of future CBF in older adults.

1. Introduction

In older adults subjects to cardiovascular risk, low cerebral blood flow (CBF) has been associated both with age-related neurodegenerative diseases such as vascular dementia and Alzheimer's disease (Schuff et al., 2009; Yoshikawa et al., 2003), and also increased risk of all-cause mortality (Sabayan et al., 2013). This would suggest a chain of events in which cumulative exposure to cardiovascular risk factors over time leads to CBF changes, which in turn increase vulnerability to adverse health outcomes, including not only cardiovascular diseases (CVDs) per se but also neurodegenerative ones, and decreased life expectancy due to all causes. As cardiovascular risk factors are largely reversible, this may constitute an effective way to reduce pathogenic changes associated with abnormal CBF levels.

* Corresponding author at: Department of Neuroradiology, University Hospital Center, Gui de Chauliac Hospital, 80 Avenue Augustin Fliche, 34295 Montpellier Cedex 5, France. Tel.: 00 334 67 33 0673; fax: 00 334 67 33 0674.
E-mail address: jeremy.deverdun@neuf.fr (J. Deverdun).

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In this context, it is important to determine which cardiovascular risk factors carry the highest risk of CBF modification. Arterial spin labeling provides a quantitative and noninvasive measurement of gray matter (GM) CBF (van Gelderen et al., 2008) yielding similar results to positron emission tomography (Arbeláez et al., 2013).

The present study aimed to assess in a cohort of healthy older adults the influence of cardiovascular risk factors, as evaluated longitudinally over a 12-year period, on global measures of CBF assessed at 12 years from baseline.

2. Materials and methods

2.1. Population

The data were derived from the prospective Montpellier-Three-City study (3C Study Group, 2003) in which healthy older adults volunteers (age >65-year old), underwent a standardized evaluation with a face to face interview, and a clinical examination at baseline (1999–2001). The ancillary Cognitive REServe and Clinical ENDOphenotype (CRESCENDO) study initiated by the National Institute of Health and Medical research and carried out in the Human Functional Imaging Institute (I2FH, Montpellier University Hospital, France) was selected specifically to identify magnetic resonance imaging (MRI) biomarkers of cognitive reserve.

Volunteers selected to participate in the CRESCENDO study were free of dementia. Baseline diagnosis of dementia was based on a 3-step procedure (3C Study Group, 2003). First, trained psychologists administered a battery of neuropsychological tests (Akbaraly et al., 2009). Second, all the participants were examined by a neurologist. Finally, an independent committee of neurologists reviewed all potential prevalent and incident cases of dementia to obtain a consensus on its diagnosis and etiology according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994). Similar procedures were performed at the 5 next follow-ups for incident dementia screening. Cases of AD were classified according to the NINCD–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and cases of mixed and/or vascular dementia according to the NINCDS–AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences) criteria (Akbaraly et al., 2009). At 12-year follow-up, participants free of dementia were invited to undergo a high-resolution MRI and complementary clinical examination as part of the CRESCENDO study (n = 380, 67.3% women, mean age of 81.96 ± 3.82-year old). The study protocol was approved by the ethics committee of the University-Hospital of Bicêtre and written informed consent was obtained from each participant.

2.2. Assessment of cardiovascular risk factors

Health behavior was assessed at baseline and consisted of smoking status (non/former/current smoker) and alcohol consumption (null/moderate/important) (Akbaraly et al., 2011; Carriere et al., 2014). Health status was ascertained at 12-year of follow-up by self-reported history of CVD (Akbaraly et al., 2011). Antecedents to be reported included stroke, angina pectoris, myocardial infarction, coronary surgery, coronary angioplasty, and arterial surgery of the legs for arteritis (Akbaraly et al., 2011; Carriere et al., 2014). Note that no participant reported antecedents of stroke.

Both at baseline and at 10 years of follow-up, information on weight, height, and use of medication were collected; fasting blood glucose, total-, high density lipoprotein-, low density lipoprotein-cholesterol, and triglycerides were measured as described in the study by Akbaraly et al. (2011). Based on these data, participants with dyslipidemia were defined as those with total cholesterol above 6.2 mmol/L or those using lipid-lowering drugs (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2001). Change in cholesterol (ΔChol), body mass index (ΔBMI), and glycemia (ΔGlyc) was assessed using the 2 available points (2 and 10 years) using $\Delta\text{Factor} = (\text{Factor}_0 - \text{Factor}_{10})/(\text{Factor}_0)$.

At the baseline clinical examination, 2 separate blood pressure measures in a seated position were performed in all participants, the first one before and the second one during the interview, using a digital electronic tensiometer (OMRON M4), and the mean of the 2 was computed. In the few cases where the 2 measures were not available, the single measure has been considered.

During follow-up, systolic and diastolic blood pressure were measured again at 2, 4, 7, 10, and 12 years. Mean arterial pressure (MAP) was retrieved from the systolic and diastolic arterial pressure using the formula: $\text{MAP} = ([2 \times P_{\text{diastolic}}]+P_{\text{systolic}})/3$. For cross-sectional analysis, MAP at 12 years was used. Pulse pressure was also retrieved using the difference between systolic and diastolic pressure. Change in MAP (ΔMAP), systolic pressure (ΔSBP), diastolic pressure (ΔDBP), and pulse pressure (ΔPP) were calculated as the linear fit slope of the variables across all available time points.

Hypertension was defined from systolic and diastolic blood pressure, respectively, above 140 and 90 mmHg or from the use of antihypertensive drugs. Please note that each time we do not refer to an evolution, we will refer to the last available time point, which is the 10 years of follow up for biological data and 12 years for the others parameters.

2.3. MRI acquisition

Neuroimaging data were collected on a 3T magnet (Skyra, Siemens, Germany) with a 32 channels head coil. Structural images (3DT1) were acquired with the parameters: field of view = 25 × 25 cm, echo time (TE) = 2.5 ms, repetition time (TR) = 1690 ms, flip angle = 9°, voxel size = 0.98 × 0.98 × 1 mm^3, 176 slices. Fluid-Attenuated Inversion Recovery (FLAIR) image was acquired to estimate white matter (WM) lesions with the following parameters: field of view = 22 × 22 cm, TE = 111 ms, TR = 7000 ms, flip angle = 150°, voxel size = 0.86 × 0.86 × 3 mm^3, 39 slices. CBF data were acquired using a 2D-pulsed arterial spin labeling sequence, PICORE-Q2TIPS (Luh et al., 1999), TI1/TI2/TR/TE = 700/2000/3000/20 ms, 52 repetitions, 16 slices (1.5 mm gap), voxel size = 3.44 × 3.44 × 6 mm^3.

2.4. FLAIR and T1 processing

Volumetric T1 and FLAIR images were checked for major signal abnormalities, using Myrian (Myrian Expert VL, Intrasense, France).

The preprocessing was performed using a custom MATLAB code (the MathWorks, Natick, MA, USA) and SPM8 (Statistical Parametric Mapping; the Wellcome Trust Center for Neuroimaging, UK), and all images were reoriented according to the anterior commissure.

The frequency of WM hyperintensities increases with advancing age (Awad et al., 1986), it was therefore important to take them into account in our processing. Owing to their intensity on T1, they may be erroneously segmented as GM. Thus, WM hyperintensities were segmented using the SPM Lesion Segmentation Tool toolbox (Schmidt et al., 2012). Using the same tool, areas identified as WM hyperintensities on FLAIR and responsible of hypointense lesions on T1 were filled by the mean global WM intensity of the subject.

Standard SPM segmentation was then performed on T1 to extract GM, WM, and cerebrospinal fluid posterior probability. Finally, segmentations were coregistered to mean arterial spin labelling image.

2.5. Arterial spin labelling processing

Arterial spin labeling images were realigned according to the baseline magnetization M_0 image acquired with a long repetition time.

Participants with major movements or artifacts were removed. The label images were then subtracted pairwise from the time matched control images using surround subtraction, to produce perfusion-weighted images. Finally, averaging is performed to get a single perfusion-weighted image.

To ensure a correct estimation of the CBF, Asllani's et al. partial volume effects (PVE) correction (Asllani et al, 2008) was applied in native space, using a 7 × 7 × 1 voxel regression kernel.

CBF computation was performed using a 1 compartment model (Wang et al., 2003):

$$CBF = \frac{\lambda.\Delta M}{2\alpha M_0 TI_1 exp\left(\frac{-TI_2}{T1_a}\right)}$$

where ΔM is the signal intensity mean difference between label and control images, λ the blood and/or tissue water partition coefficient, $T1_a$ the longitudinal relaxation time of blood, α the inversion efficiency, and M_0 the blood magnetization.

We chose to use the estimation of GM ΔM and M_0 given by the PVE correction to compute the GM CBF. The blood magnetization (M_0) was estimated using the local tissue method (Cavuşoğlu et al., 2009).

The parameters used for the quantification were labeling efficiency = 0.95; longitudinal relaxation, $T1_a$ = 1664 ms; and as we focused on GM, λ_{GM} = 0.98.

2.6. Image quality control

After realignment, participants presenting major movements or missing images were removed from analysis (n = 17). Then, before averaging, perfusion-weighted images were labeled as unusable if containing more than 50% of negative values. Participants with more than 20% of unusable perfusion-weighted images were excluded from subsequent analysis (n = 224; Fig. 1). For remaining participants, mean difference was obtained by averaging the remaining perfusion images.

After quantification, we further excluded from analysis the participants for whom the labeling was clearly inhomogeneous, in the absence of signal abnormalities on FLAIR sequences that could explain perfusion heterogeneity (n = 16; Fig. 1). Eventually, from the 380 participants originally included in the CRESCENDO project, 104 only had data suitable for CBF estimation.

From a methodological point of view, this large number of excluded participants may question the capacity of arterial spin labeling (ASL) to provide valid CBF quantification in older adults. We claim (see Section 4 Discussion) that this is the consequence of the selection of a single inversion time for all participants.

To validate this hypothesis, we performed test acquisitions on 6 healthy participants selected in our institute (mean age 24.5 ± 2 year-old) assuming that the effects of incorrect inversion time on young and older adults are the same regarding unusable perfusion-weighted images. Multiple arterial spin labeling acquisitions were performed using the same parameters used in our cohort but with varying inversion time (1300, 1400, 1500, 1600, 1700, 1800, 1900, and 2000 ms). To estimate the bolus arrival time, an additional 3D-GRASE arterial spin labeling acquisition (Günther et al., 2005) was performed using 16 inversion time (ranging from 480 to 4000 ms) with the parameters bolus duration 700 ms, TR = 3000 ms, TE = 20 ms, parallel imaging factor = 2, 24 slices, voxel size = 3.4 × 3.4 × 4 mm^3. Bolus arrival time maps were generated online using the Siemens automatic pipeline. A radiologist identified the real optimal inversion time by drawing circular regions of interest in GM of different vascular territories on bolus arrival time map for each participant.

2.7. Data extraction

Mean GM CBF was retrieved from PVE-corrected CBF map by applying the GM posterior probability (threshold = 0.8) obtained from T1 segmentation.

2.8. Statistical analysis

Skewed variables (CBF) were log-transformed to normalize their distribution before statistical analyses.

A first set of analyses were conducted to examine the CBF differences according to sex and age. Mean comparisons using Student *t*-test were performed to compare global and regional CBF measures between men and women.

Correlation analyses (Pearson's correlation coefficient) have been performed to examine the association between age and CBF measures.

To assess the association between cardiovascular risk factors assessed at baseline, or their change over the follow-up and CBF measures, linear regression models were performed adjusted for sex and age.

The *p*-values below 0.0022 (0.05 corrected for multiple comparisons using a Bonferroni's correction) were considered to be statistically significant. Analyses were performed using R software, version 3.0.2.

3. Results

The mean CBF value across the entire GM volume was 45.2 ± 10.6 mL/100 g/min. Detailed results of the statistical analysis performed are presented in Table 1. Note that we also performed regional analysis which are reported as Supplementary materials; they do not present further significant results.

3.1. Sex and age

Women showed significant higher CBF levels than men (women: 47.2 ± 10.8 mL/100 g/min and men: 41.3 ± 9.4 ml/100 g/min; see details in Electronic Supplementary Material). Age was not correlated to CBF (Table 1).

3.2. Health behaviors

No association was found between smoking status and alcohol consumption assessed at baseline and CBF levels assessed 12 years later.

3.3. Diabetic status and blood glucose

We did not find significant association between type 2 diabetes (13 patients) and CBF. However a trend of a reduced CBF with high levels of fasting blood glucose was found ($p = 0.05$, $R^2 = 0.10$).

Similarly, the analysis of longitudinal data shows a trend to a reduced CBF with increasing glycemia ($p = 0.04$, $R^2 = 0.10$).

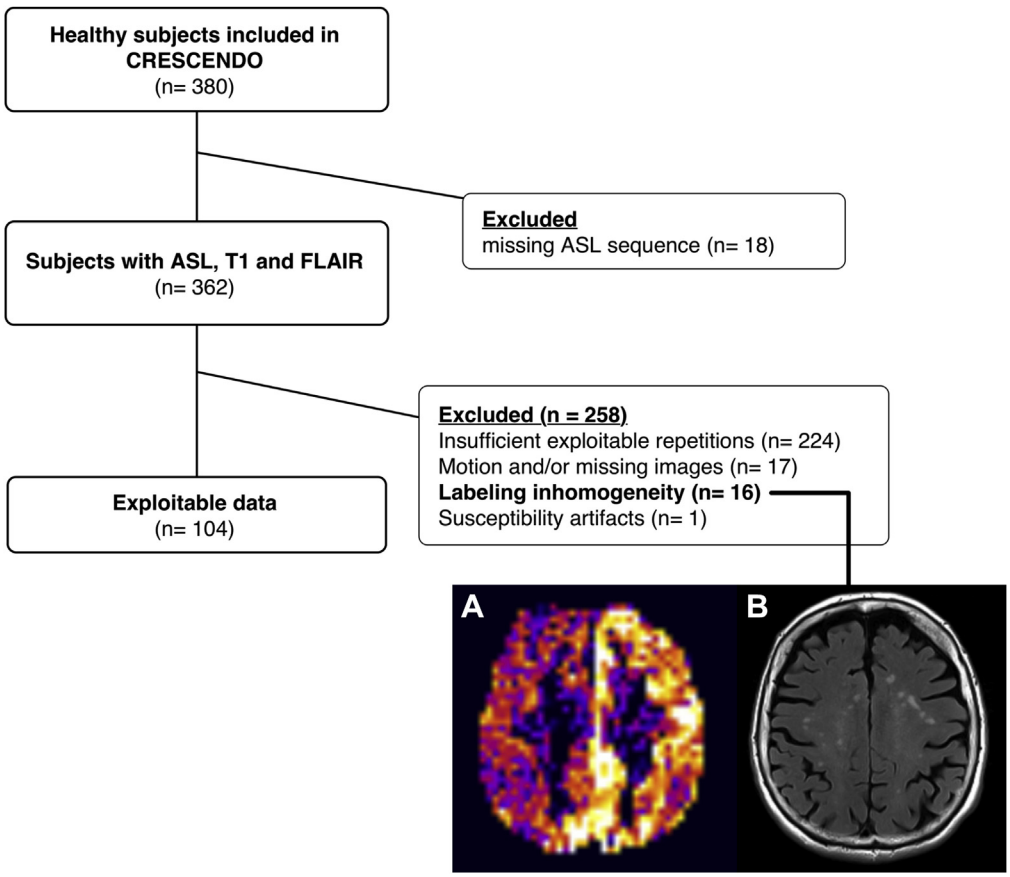


Fig. 1. Flow charts showing of the participants' selection. Participants who did not fit the requirements (missing data, major artifacts, and so forth) were excluded. Perfusion-weighted images were checked and labeled as unusable when they contained more than 50% of obvious artifacts such as negative values. Participants with more than 20% of perfusion-weighted images identified as unusable were excluded from subsequent analysis (n = 224). An example of the inhomogeneity issue is display, on the left (A), the CBF map, and on the right the corresponding FLAIR image (B). Although there is a clear signal difference between left and right hemisphere on CBF map, no evidence of pathology is visible on FLAIR. Abbreviations: CBF, cerebral blood flow; CRESCENDO, Cognitive REServe and Clinical ENDOphenotype; FLAIR, fluid-attenuated inversion recovery.

3.4. Dyslipidemia status and blood lipids

Neither dyslipidemia status nor total cholesterol was associated with CBF. Increase or decrease in cholesterol (ΔChol) over 10 years was not correlated to CBF.

3.5. Body mass index

Body mass index did not exhibit any link with CBF in neither cross-sectional nor longitudinal analysis.

3.6. Hypertension status and MAP

For hypertension, no association was observed with CBF.

No observable association between baseline or follow-up MAP values and mean CBF was detected (Fig. 2A). The same result holds regarding systolic, diastolic, and pulse pressure.

Increased MAP over 12 years was associated with lower CBF across the whole GM ($p < 0.0022$, $R^2 = 0.21$, Fig. 2B). Evolutions of systolic and diastolic blood pressure exhibit the same trend, although there is a statistical significance loss after Bonferroni's correction ($p = 0.004$, $R^2 = 0.19$ and $p = 0.01$, $R^2 = -0.09$, respectively).

3.7. Self-reported CVDs

No significant trends were observed in global CBF values between participants who self-reported CVD compared with those who did not.

3.8. Population selection bias

Differences in characteristics between our sample and the excluded participants (based on the CBF quantification quality criterium) were examined and given in Table 2.

Participants retained for our analysis exhibit a significant difference compared with the whole group in term of glycemia value, as well as its evolution ($p < 0.01$, Table 2).

BMI and ΔBMI were also found significantly different between excluded participants and retained sample ($p < 0.01$).

4. Discussion

This study investigated the relationship between long-term evolution of cardiovascular risk factors and cerebral perfusion acquired at 1 time point, in an epidemiological cohort study of healthy older adults. Using arterial spin labeling methods, global GM CBF has been estimated, with values in agreement with those observed in other reports (Brumm et al., 2010; Chen et al., 2011), including differences according to sex.

More specifically, our findings showed that among the cardiovascular risk factors, only change in MAP was strongly associated with CBF.

4.1. Blood pressure

One of the major finding of this study is the association between MAP and CBF. In coherence with recent findings

Table 1
Results of the statistical analysis of the correlation of cerebral blood flow (CBF) and various factors

Factors	*p*-value	R^2	β	Standard error
Age	0.88	NA	NA	NA
Sex	**0.002***	NA	NA	NA
Systolic pressure	0.53	0.06	−0.0008	0.001
Evolution of systolic pressure	**0.004**	0.19	−0.06	0.02
Diastolic pressure	0.12	0.08	−0.004	0.002
Evolution of diastolic pressure	**0.01**	0.15	−0.09	0.04
Mean arterial pressure	0.16	0.10	−0.003	0.002
Evolution of mean arterial pressure	**0.002***	0.21	−0.1	0.03
Pulse pressure	0.83	0.06	0.0003	0.001
Evolution of pulse pressure	0.06	0.13	−0.04	0.02
Hypertension	0.73	0.05	−0.02	0.05
Diabetes	0.53	0.06	−0.04	0.07
Glycemia	**0.04**	0.10	−0.06	0.03
Evolution of glycemia	**0.05**	0.10	−0.38	0.19
Dyslipidemia	0.30	0.08	0.05	0.05
Cholesterol	0.24	0.08	−0.03	0.02
HDL	0.31	0.07	0.07	0.07
LDL	0.20	0.08	−0.03	0.03
Triglycerides	0.09	0.09	−0.07	0.04
Evolution of cholesterol	0.69	0.06	−0.0005	0.001
Body mass index	0.59	0.05	0.005	0.008
Evolution of body mass index	0.47	0.06	−0.23	0.32
Alcohol	0.94	0.05	−0.003	0.04
Smoking	0.60	0.05	0.02	0.04
Cardiovascular disease	0.78	0.05	−0.02	0.06

Age results were obtained from a Pearson correlation, a 1 tailed *t*-test was used for gender, and for the others parameters, multivariate linear regression with adjustment on gender and age was used. Significance is indicated by *p* (*p*-value), adjusted R^2, β, and standard error are also reported when available, *p*-values are bold if inferior or equal to 0.05. Significant association on CBF after correction for multiple comparisons (Bonferroni's corrected *p*-value: 0.0022) are displayed with a star.
Key: HDL, high density lipoprotein; LDL, low density lipoprotein.

(Foster-Dingley et al., 2015), neither hypertension status nor MAP, systolic, or diastolic blood pressure were associated with CBF. Only MAP long-term evolution was associated to CBF, and not baseline nor follow-up values. This rules out the possibility that some initial or final health status of the participants is the source of the effect.

To maintain consistent CBF in the face of variability in MAP, the brain adapts its vasculature through a group of mechanisms referred to as cerebral autoregulation (Paulson et al., 1990). The absence of association of CBF to MAP at 1 time point tends to reveal that these mechanisms can be preserved in healthy older adults, as was established in younger cohorts (Lipsitz et al., 2000; Oudegeest-Sander et al., 2014; van Beek et al., 2008). Rather than the MAP baseline value or its measurement at the 12-year follow-up, it appears that the major factor that affects the CBF is the 12-year evolution (ΔMAP). Our results show that increase in MAP (ΔMAP >0) is associated to lower CBF and that decreasing MAP is correlated to higher CBF. The evolutions of systolic blood pressure, and to a lesser extent of diastolic blood pressure, are similar to ΔMAP in terms of association with CBF, although loosing significance after Bonferroni's correction.

It is well-known that CVDs can be associated with long-term changes in cerebral autoregulation. Chronic hypertension is known to shift to higher values the pressure range associated to CBF stability (Traon et al., 2002). Older adults are moreover known to have a lower stable CBF value than mid-age individuals.

Our results show that in healthy older subjects, long-term MAP evolution (and not single time MAP measures) could be inversely associated to stable CBF values. Interestingly, we observe that for negative ΔMAP, CBF values are then closer to those observed in mid-age.

Previous studies have suggested this relation between CBF and MAP changes in older adults with blood pressure lowering therapy (Lipsitz et al., 2005; Tryambake et al., 2013). Based on this and our results, it is possible that observations obtained from intensive medication (Lipsitz et al., 2005; Tryambake et al., 2013) can occur in standard conditions (without medication) but with longer delays.

Of course, it is important to note that evolution of MAP could be an effect of the antihypertensive drugs. Nevertheless, in our cohort, less than a third of the participants began a treatment during the study, and none stopped their hypertensive medication. We investigated differences in the evolution of MAP between stable participants (regarding the treatment) and newly treated ones, but these groups are statistically similar (2 tailed *t*-test, $p = 0.72$).

Note also that pulse pressure and its evolution were not associated with CBF. This result was expected, as both systolic and diastolic blood pressures have the same trend of association with CBF (inversely associated to CBF).

4.2. Sex and age

Our observed lower global CBF values in men compared with women have been previously established in older adults (Chen et al., 2011; Liu et al., 2011). It is therefore important to take into

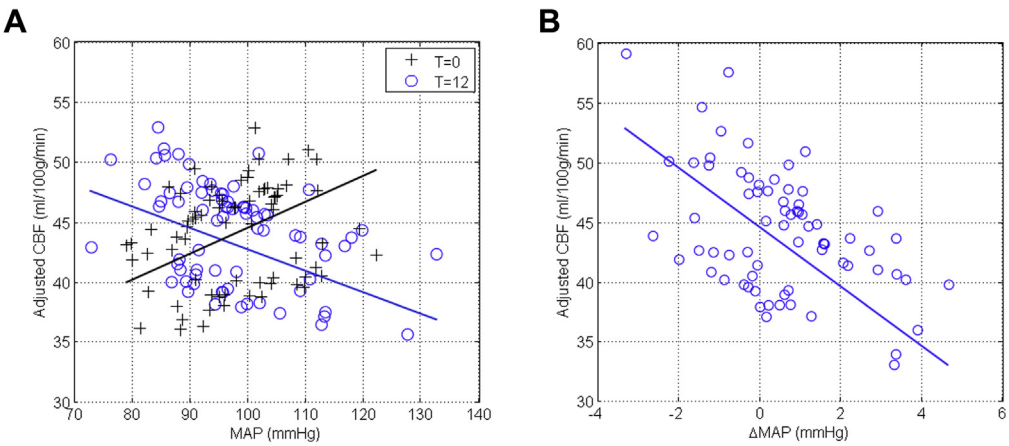


Fig. 2. Adjusted cerebral blood flow (CBF) according to baseline, final, and evolution of mean arterial pressure (MAP). (A) This shows the results of the linear model after adjustments for age and sex. The values of the MAP at baseline (T = 0) and at the magnetic resonance imaging time (T = 12) are displayed as black crosses and blue circles with their respective regressions. No significant associations were found between those factors and the CBF ($p > 0.05$). The results with the evolution of MAP are displayed in (B). The CBF was significantly associated to evolution of MAP ($p = 0.002$).

Table 2
Characteristics of study participants in the whole study and sample used

Characteristics	Excluded participants		Usable data		*p*-value
	Value	Availability	Value	Availability	
Sociodemographic factors					
Male	134 (48.5 %)	276	34 (32.7 %)	104	**0.005**
Age, y	82.25 (3.97)	276	81.3 (3.3)	104	**0.03**
Cognitive status					
MMSE	28.45 (1.61)	270	28.78 (1.35)	101	0.07
NART	22.54 (5.77)	273	22.28 (5.86)	102	0.70
Alcohol consumption					
None, n (%)	34 (12.8 %)	266	13 (12.7 %)	102	0.57
Moderate, n (%)	172 (64.7 %)	266	71 (69.6 %)	102	0.57
High, n (%)	60 (22.6 %)	266	18 (17.6 %)	102	0.57
Smoking status					
Nonsmoker, n (%)	164 (59.4 %)	276	70 (67.3 %)	104	0.35
Former smoker, n (%)	93 (33.7 %)	276	29 (27.8 %)	104	0.35
Current smoker, n (%)	19 (6.9 %)	276	5 (4.7%)	104	0.35
Biological data					
BMI, kg/m^2	24.72 (3.39)	274	23.2 (2.76)	103	**<0.001**
ΔBMI	0.002 (0.08)	265	−0.02 (0.07)	103	**0.008**
Glycemia, mmol/L	5.46 (0.93)	236	5.17 (0.71)	90	**0.007**
ΔGlyc	−0.10 (0.16)	236	0.08 (0.12)	90	**<0.001**
Diabetic status, n (%)	43 (18 %)	238	13 (14.1%)	92	0.39
HDL, mmol/L	1.55 (0.37)	235	1.62 (0.36)	90	0.08
LDL, mmol/L	3.40 (0.93)	235	3.46 (0.88)	90	0.6
Triglycerides, mmol/L	1.27 (0.52)	235	1.20 (0.53)	90	0.3
Total cholesterol, mmol/L	5.53 (1.08)	235	5.64 (1.04)	90	0.41
ΔChol	0.04 (0.2)	235	0.05 (0.19)	90	0.61
Dyslipidemia, n (%)	147 (60 %)	245	56 (53.8%)	95	0.86
Cardiovascular factors					
MAP, mmHg	96.73 (11)	269	96.7 (10.9)	91	0.99
ΔMAP	−0.03 (1.03)	209	0.23 (0.82)	71	**0.05**
Systolic blood pressure (SBP)	142 (17.6)	269	143.7 (18.36)	91	0.42
ΔSBP	0.65 (1.66)	209	1.05 (1.39)	71	0.06
Diastolic blood pressure (DBP)	74 (10.3)	269	73.4 (9.4)	91	0.55
ΔDBP	0.37 (0.95)	209	−0.18 (0.7)	71	0.11
Pulse pressure (PP)	67.95 (15.4)	269	70.3 (16.27)	91	0.16
ΔPP	1.01 (1.23)	209	1.23 (1.17)	71	0.19
Hypertension, n (%)	215 (78.75 %)	273	75 (73 %)	103	0.22
Hypertension treatment, n (%)	153 (55.64 %)	275	48 (46.6 %)	103	0.12
Cardiovascular disease, n (%)	67 (24.63 %)	275	20 (19.4 %)	103	0.31

Description of the full CRESCENDO cohort and sample taken for this study after removal of participants with unusable data. Were assessed at baseline: alcohol consumption, NART (National Adult Reading Test), and smoking status. At 10 y, biological data (except BMI). At 12 y, BMI, and cardiovascular factors. Data are expressed as mean and standard deviation except as noted. Number of available observations of each variable is displayed. Differences between the initial cohort and our sample is investigated through χ^2 test or 2 sample *t*-test. *p*-values in bold highlight a significant difference between the groups according to a 0.05 threshold.
Key: BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; MAP, mean arterial pressure; MMSE, mini-mental state examination.

account this variable as confounding factor in CBF-related studies. Men have a lower life expectancy. and it has been shown that lower CBF is associated to an increase risk of all-cause mortality (Sabayan et al., 2013).

As sex, aging effect on CBF is well-documented both using arterial spin labeling and positron emission tomography (Chen et al., 2011; Martin et al., 1991). Nevertheless, we were not able to see any association between age and CBF in our cohort. This null finding might be due to the age homogeneity of our cohort, preventing the observation of any statistically significant age-dependent effect.

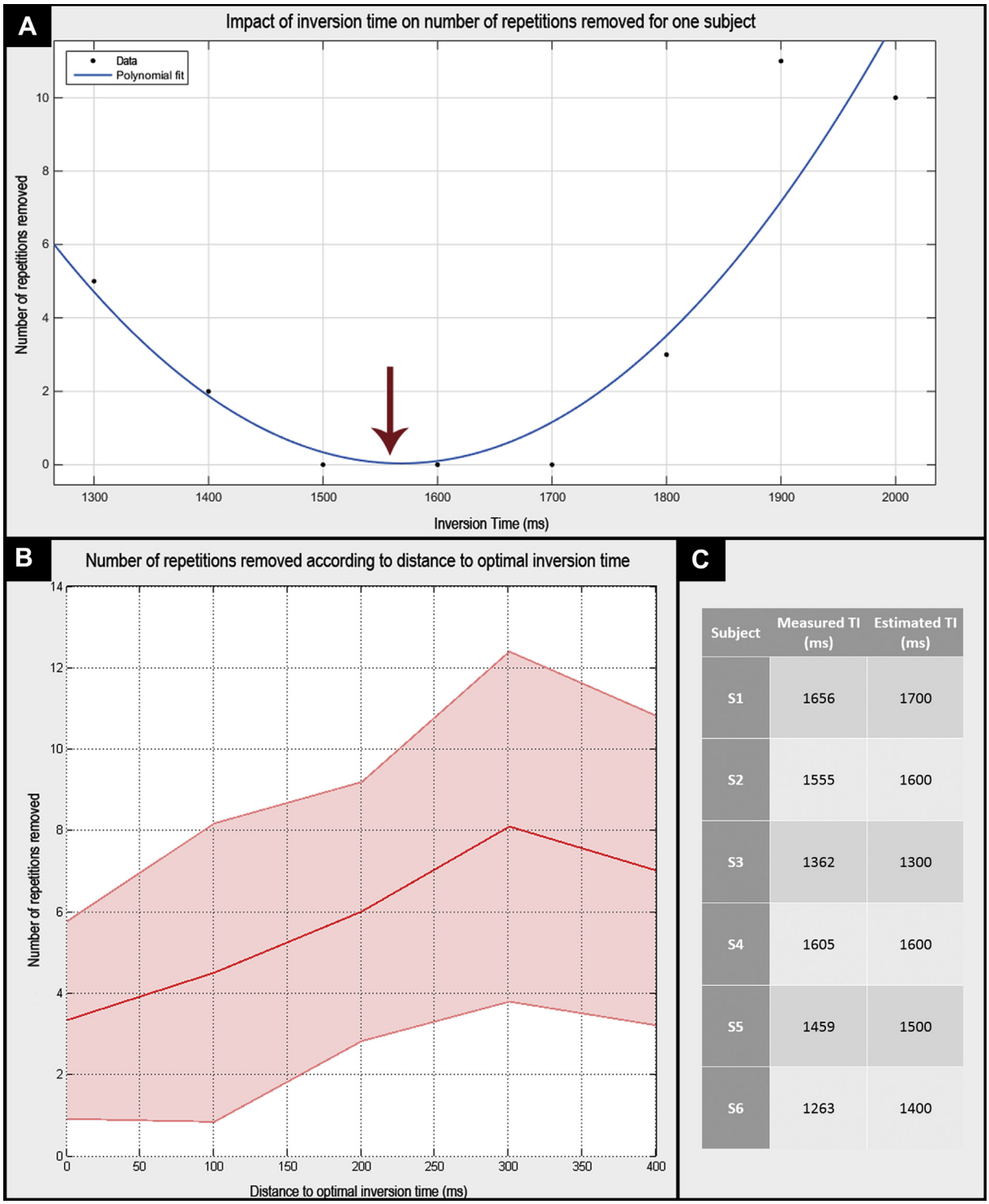
4.3. Diabetes and glycemia

Diabetes has been shown to reduce cerebrovascular reactivity (Dandona et al., 1978; Fülesdi et al., 1997). The absence of association between type 2 diabetes and CBF values might be due here to a power, with only 13 cases of type 2 diabetes. Glycemia levels and their evolution, although not significant after Bonferroni's correction, show a negative trend with CBF. Low levels of glycemia have been associated to an increased CBF (Arbeláez et al., 2013), and reciprocally hyperglycemia is related to a decreased CBF (Duckrow, 1995). High levels of glycemia may increase arterial stiffness through alteration of the arterial wall (Rubin et al., 2012). Moreover, increased arterial stiffness is known to be associated with increased cerebrovascular resistance and reduced CBF (Kielstein et al., 2006; Lipsitz et al., 2005; Robertson et al., 2010).

Nevertheless, as explained in the methodological discussion in the following, excluded participants because of ASL quantification issues had significantly higher glycemia levels. This, of course, induces a bias in our sampling because it prevents us from including most of the high glycemia participants and may explain the weak correlation we observed.

4.4. Other variables

In previous studies, decreased CBF were observed with increasing BMI (Willeumier et al., 2011), chronic alcohol consumption (Christie et al., 2008), and cigarette smoking (Kubota et al., 1983). We were not able to see any correlation between those factor and CBF. The explanation is that, like age, their range of values in our sample is narrow. The 2-year gap between the last assessment of these biological data and the MRI examination should also be kept in mind and is a limitation on our conclusions.



Subject	Measured TI (ms)	Estimated TI (ms)
S1	1656	1700
S2	1555	1600
S3	1362	1300
S4	1605	1600
S5	1459	1500
S6	1263	1400

Fig. 3. Impact of inversion time (TI) on number of removed repetitions. Pertinence of our quality control criteria is investigated. In (A), the number of repetitions that have been removed according to our criteria is displayed for 1 subject for multiple inversion time. The dots correspond to the real value, the blue curve is a second degree polynomial fit on the data, and finally, the red arrow highlight the optimal inversion time identified on the bolus arrival time map (1555 ms). The value measured on the map is concordant with the minimum of the curve. (B) This shows the average number of removed repetitions for all participants according to the absolute distance of the inversion time to the optimal one. The center red line is the average, the top and bottom lines show the standard deviation. When the distance to the optimal inversion time increases, the number of repetitions that have to be removed is increased. (C) This shows the optimal inversion time (in ms) identified by drawing regions of interest on bolus arrival time map ("measured TI") compared with the inversion time with the less number of removed repetition for each participants ("estimated TI"). The 2 values are very close. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Finally, no clear association between self-reported cardiovascular events and CBF was found. We nevertheless have to keep in mind that our participants' recruitment in itself selects a healthy population. Indeed, the prevalence of cardiovascular events in our group is far below the average for participants of this age (American Heart Association, Inc, 2013).

4.5. Limitations and methodological remarks

The main strengths of this study include (1) a large cohort; (2) a long follow-up time of 12 years; and (3) availability of extensive data on cardiovascular risks factors. Our conclusions have nevertheless limitations due to various factors.

The first limitation comes from the cohort selection of "highly" healthy older adults, which prevents generalization of our findings to the general population of older adults. Indeed, we know that there is a far higher prevalence of CVDs and risk factors in this age range in the general population.

Moreover, note that we only had access to late-life vascular risk factors information. Yet, it has been shown that mid-life risk factors are more influential (Roberts et al., 2015).

For some factors such as diabetic status or particular CVDs, the lack of statistical power in our cohort could explain the absence of correlation with CBF.

Finally, we have to remember that we only have 1 measure of the CBF at 12 years. Although we observed associations between specific factors and the CBF values, at least 1 additional perfusion acquisition would be required to assess their relation to CBF change.

The last crucial methodological point concerns the exclusion of large number of participants due to CBF quantification issues, and its influence on our conclusions.

Currently, very few studies have been performed on cohorts of older adults (mean age >80-year old) using arterial spin labeling. In our case, this acquisition was the last sequence of a long protocol, and after more than 45 minutes, participants can be tired and exhibit increased motion. Moreover, we were constrained by coherence across the study to use a single inversion time for all participants, which could be inadequate due to arterial transit time variations. These factors, together with labeling inhomogeneity or the presence of surgical clips, are known to alter the quality of CBF quantitative measurement (Alsop et al., 2014). Thus, a particular care had to be taken, through the use of a strict objective criterium described in the Materials and methods Section, to prevent the use of corrupted data. As a consequence of this strict threshold for inclusion, an important number of participants had to be removed.

Among the excluded participants no sign of major motion or labeling inhomogeneity was identified. In addition, no participants had surgical clip that could explain those errors. Our further analysis suggests that inappropriate inversion time is the main factor for the large exclusion number.

Optimal inversion time is closely associated to medical history (Campbell and Beaulieu, 2006) and can strongly vary in older adults. As shown on Fig. 3B from our test data on younger adults, when the sequence inversion time varies, the number of removed (>50% negative values) repetitions goes through a minimum. Let us define the optimal inversion time as the one leading to the lowest number of removed repetitions. So defined, it can be shown in our young adults group (Fig. 3A and C) to coincide with the real one, as obtained from an independent 3D multi-inversion time ASL protocol. Taken together, these results support the hypothesis that the incorrect inversion time is the main factor for repetitions removal.

This creates a specific problem for ASL studies involving older adults, and our study is to our knowledge the first one to be based on a large cohort of such participants. Indeed, for younger adults, transit time do not exhibit the same variability (Campbell and Beaulieu, 2006), which explains that the application of a rigorous quality criterium is not explicitly mentioned. The exceptionally large number of excluded patients in our case results from the nature of our cohort that imposes this methodological rigor.

What about the bias in our conclusions induced by this selection criterium?

Based on comparison between excluded and included participants, only BMI, glycemia, age, and sex appear indeed to be significantly different. Note that among these factors, BMI, age and sex have been shown to modify the arterial transit time, in agreement with our hypothesis (Liu et al., 2011; MacIntosh et al., 2014). Glycemia has not been investigated in that respect.

But do we bias the measured CBF values themselves? It is hard to speculate on the excluded population CBF values. We can only be assured that the data we select are the only usable part of our whole ASL data set and that the extracted CBF values are coherent. The criterium we applied in selecting our exclusion threshold was based on the coherence of the CBF values: among participants for which less than 20% of repetitions have been excluded there is no association (Pearson correlation, $p > 0.05$) between the number of repetition excluded and the measured CBF values). Such artefactual correlation exists for excluded data (Pearson correlation, $p < 0.05$), only due to the fact that when negative artefactual values are present (which we eliminate), positive artefactual values are also present, which contribute to a global artefactual increase in the CBF measure. For the excluded participants, we thus just cannot access the CBF values and cannot rule out the possibility that the corresponding CBF, if correctly measured could modify our results. We only have no hints regarding the possible origin of such a bias. Other studies dedicated to large cohorts of older adults are obviously necessary, using multi-inversion time ASL or other perfusion techniques, to further investigate the association between cardiovascular risks and cerebral blood flow.

5. Conclusion

The main strengths of this study are the availability of CBF mapping for an unusually large number of older adults, along with sociodemographic and cardiovascular factors across a 12-year period.

Our findings suggest that evolution of MAP is the most meaningful factor to take into account in older adults to reduce risks related to low CBF. In addition, our work highlighted the importance of quality check with this kind of population.

Disclosure statement

All the authors report no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.05.012.

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