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ORIGINAL ARTICLE

Ageing affects the balance between central and peripheral mechanisms of cerebrovascular regulation with increasing influence of systolic blood pressure levels

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Abstract

Background Arterial baroreflex (BR) and cerebral autoregulation (CA) are two major regulatory mechanisms that maintain constant cerebral perfusion. Little is known about the interplay between these mechanisms, particularly when considering the effects of ageing or sex.

Purpose We studied the relationship between dynamic CA and BR sensitivity (BRS) in healthy subjects by sex and in different age strata.

Methods 95 healthy adults (52% female), 20–80 years-old, were recruited. Arterial blood pressure (Finometer), 3-lead electrocardiogram and cerebral blood flow velocity in middle cerebral arteries (transcranial Doppler) were monitored. We assessed CA by transfer function analysis and BRS in frequency and time domain.

Results With increasing age, BRS diminished (ANCOVA $R^2 = 0.281$, $p < 0.001$) but CA parameters did not change significantly ($p > 0.05$). Overall, there was an inverse relationship between the efficacy of BRS and CA low-frequency gain [multivariate linear regression $\beta = 0.41$ (0.31; 0.61), $p < 0.001$]. However, this association suffers changes with ageing: in older subjects BRS and CA were not correlated [$\beta = 0.10$ (−0.41; 0.62), $p = 0.369$]. Instead, decreasing systolic blood pressure correlated with less efficient CA [lower CA low-frequency gain $\beta = -0.02$ (−0.03; −0.02), $p = 0.003$]. Sex did not affect BRS and CA relationship.

Conclusions Cerebral blood supply is governed by a tuned balance between BR and CA which is lost with age as BRS decreases dramatically. Low systolic blood pressure values might be harmful to older subjects as they might reduce the ability to keep cerebral blood flow tightly controlled.

Keywords Ageing · Sex · Cerebral autoregulation · Arterial baroreflex · Autonomic nervous system

Abbreviations

ABP	Arterial blood pressure
BR	Baroreflex
BRS	Baroreflex sensitivity
CA	Cerebral autoregulation
CBFV	Cerebral blood flow velocity
CrCP	Critical closing pressure
CVRi	Cerebrovascular resistance index
DBP	Diastolic blood pressure
HF	High-frequency spectral band
HR	Heart rate
HRV	Heart rate variability
LF	Low-frequency spectral band
MBP	Mean ABP
MCA	Middle cerebral artery
PP	Pulse pressure
RAP	Ratio-area-product

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SBP	Systolic blood pressure
SDNN	Standard deviation of normal RR intervals
TCD	Transcranial Doppler
TFA	Transfer function analysis
VLF	Very-low frequency spectral band
xBRS	Time domain cross-correlation BRS
α-index	Frequency domain BRS gain

Introduction

Maintaining safe levels of cerebral perfusion is essential for cerebral function, with both insufficient and excessive blood perfusion being harmful (Azevedo and Castro 2016). Thus, regulatory mechanisms act to maintain an adequate nutrient and oxygen supply to the brain, even under considerable external changes, in a complex network which integrates both intrinsic and extrinsic pathways (Willie et al. 2014; Azevedo and Castro 2016).

Baroreflex (BR) is an extrinsic reflex loop entailing cardiac, vascular and cerebral components responsible for short-term systemic blood pressure regulation (Ogoh et al. 2008; Lantelme et al. 2002). Changes in arterial blood pressure (ABP) are sensed by baroreceptors, located on the wall of the carotid arteries and aorta, which adjust heart rate (HR) and vascular tone, via the autonomic nervous system, restoring ABP to baseline levels (Lantelme et al. 2002). The sensitivity of this BR (BRS) can be studied non-invasively by spontaneous oscillations of HR and ABP (Westerhof et al. 2004).

On the other hand, a major intrinsic mechanism implicated in cerebrovascular regulation is autoregulation (CA). CA refers to the intrinsic property of the brain vessels to stabilize cerebral blood flow in response to variations in ABP (Willie et al. 2014; Azevedo and Castro 2016; Claassen et al. 2016). CA is best studied non-invasively, with analytic methods such as transfer function analysis (TFA) of beat-to-beat variations of both cerebral blood flow velocity (CBFV), assessed by transcranial Doppler (TCD), and peripheral ABP (Claassen et al. 2016).

The status of CA and BR in human disease is important. A disturbed CA in subjects with ischemic stroke (Castro et al. 2017a, b, c) and cerebral small vessel disease (Purkayastha et al. 2014), may lead to the brain being excessively sensitive to fluctuations in ABP that could make outcome worse. Also, an impaired BR is correlated with more complications in myocardial infarction and chronic heart failure (La Rovere et al. 2008).

Since age and sex are important prognostic factors in vascular disease, it is important to understand how they affect the mechanisms that regulate the vascular tree. Despite increasing age causing vascular rigidity and decreases CBFV (Bakker et al. 2004), the various cerebral autoregulatory mechanisms seemed to be preserved with ageing (Madureira et al. 2017). BR, on the other hand, is less efficient in the older (La Rovere et al. 2008). Lastly, although the differences in autonomic neural-hemodynamic balance between sex groups reported in the literature (Hart et al. 2009), it is not clear how exactly they could affect cerebrovascular regulation (Madureira et al. 2017).

For all these reasons, despite the relation between CA and BRS being already addressed (Tzeng et al. 2010), we do not know how CA and BRS interplay along increasing age and between sexes. On this account, the literature is particularly scarce. We sought to investigate the relationship between BRS and dynamic CA, assessed by TFA, with particular emphasis on the effects of age and sex.

Materials and methods

This study was conducted in the dedicated functional cerebral hemodynamic laboratory of our institution. The local institutional ethical committee approved the study. Informed consent was obtained from all participants included in the study.

Population studied

Subjects were selected by advertising within university facilities. We selected Caucasian participants with a sex ratio 1:1 in each decade of age strata, ranging from 20 to 80 years-old. Individuals were then analysed by subgroups of young ($\leq$40 years-old), middle (41–61) and old ($\geq$61) age and also by sexes.

All participants fulfilled a comprehensive questionnaire to exclude common vascular risk factors (hypertension, diabetes, and smoking) and diseases affecting the cardiovascular, cerebral and autonomic nervous systems. Systolic (SBP), and diastolic arterial blood pressures (DBP) were measured with sphygmomanometer. MBP was calculated by the formula $MBP = 1/3 \times SBP + 2/3 \times DBP$ and pulse pressure (PP) as $PP = SBP - DBP$. Body mass index was calculated. Cervical and transcranial ultrasound examination (Vivid e, GE) excluded hemodynamically significant stenosis.

Monitoring protocol

Evaluations were carried out in a dim lighted room, ambient temperature and supine position. Subjects refrained from caffeine, alcohol or vasoactive drugs in the last 12 h before measurements. CBFV was recorded bilaterally from M1 segment of the middle cerebral artery (MCA), at depth of 50–55 mm, with 2-MHz monitoring probes (Doppler BoxX, DWL, Singen, Germany) secured with a headband. Continuous ABP was recorded with Finometer MIDI (FMS,

Amsterdam, Netherlands). We also recorded a standard 3-lead electrocardiogram and end-tidal carbon dioxide ($EtCO_2$) by nasal cannula with capnograph (Respsense Nonin, Amsterdam, Netherlands). All data were digitized at 400 Hz with Powerlab (AD Instruments, Oxford, UK) and stored for offline analysis. After resting for 20 min, a 10-min period of resting data was stored for BR and CA calculations.

Data analysis

All signals were visually inspected to identify artefacts or noise, and narrow spikes were removed by linear interpolation. For each heart-beat, systolic and diastolic values of ABP and CBFV were identified and time-averaged MBP and mean CBFV (MFV) were obtained. Two different pressure–velocity models were evaluated. Firstly, the classical cerebrovascular resistance index (CVRi) was estimated by the ratio of MBP/MFV for each heartbeat. Secondly, the instantaneous relationship between ABP and CBFV was used to estimate the CrCP and RAP of the cerebral circulation for each cardiac cycle, using the first harmonic method (Panerai et al. 1999; Castro et al. 2014). CVRi calculation assumes that there is a linear relationship between ABP and CBFV, i.e., flow ceases only when ABP is zero. CrCP has been shown to be important for cerebrovascular tone control mainly for reflecting changes due to metabolic stimulus to cerebral blood flow, like cognitive (Salinet et al. 2013), CO_2 (Panerai 2003) and intracranial pressure (Castro et al. 2014). Some evidence suggests that RAP follows physiological changes presumed to be predominantly myogenic (Castro et al. 2014; Panerai et al. 2005). No detrending technique was used because a steady state was secured for visual inspection of the signals and also to be consistent with the suggested guidelines for TFA analysis (Claassen et al. 2016).

All beat-to-beat estimates were interpolated with a third-order polynomial and resampled at 10 Hz to generate a time series with a uniform time-base. To correct for differences at baseline values and, in the case of CBFV, to become independent from the TCD insonation angle, data were also normalized by their mean baseline values.

CA calculations

Dynamic CA was assessed by TFA by calculating coherence, gain and phase parameters from beat-to-beat spontaneous oscillations in MFV and MBP with the parametrization in accordance with standard recommendations (Claassen et al. 2016). Averaged periodogram was calculated by Welch method with Hanning window of 30 s, with two-third overlap. Coherence was calculated between input auto-spectra of MBP over cross-spectra of MFV/MBP and transfer functions of phase and gain were determined by dividing the cross-spectrum by the input auto-spectrum. Coherence, gain and phase are reported in three bands: very-low (VLF: 0.02–0.07 Hz), low (LF: 0.07–0.20 Hz) and high (HF: 0.20–0.50 Hz). CA is believed to operate at slower VLF and LF bands (Meel-van den Abeelen et al. 2014; Deegan et al. 2011). In short, coherence expresses the fraction of MFV variance that can be explained by the corresponding MBP power at each frequency, varying between 0 and 1 analogous to the squared correlation coefficient and can help to identify conditions where estimates of gain and phase may not be reliable (Claassen et al. 2016). Gain quantifies the damping effect of CA on the magnitude of MBP oscillations to MFV. Phase shift represents the time delay between MBP and MFV oscillations. Lower gain and higher phase represent tighter, more effective autoregulatory response (Azevedo and Castro 2016).

Autonomic calculations

The same 10 min of resting recording were used to analyse short-term heart rate variability (HRV) and BRS in both time and frequency domains (Freitas et al. 2007). HRV was assessed in time domain using standard deviation of normal RR intervals (SDNN). On frequency domain, HRV was characterized by power spectrum of normal RR intervals, at low (LF; 0.04–0.15 Hz) and at high frequency (HF; 0.15–0.40 Hz). Spontaneous BRS was assessed in time domain by cross-correlation method (×BRS) as detailed before (Westerhof et al. 2004) which is based on the serial computation of correlation coefficients between beat-to-beat SBP and RR intervals in a sliding 10 s window. In frequency domain, BRS is commonly called α-index (Lucini et al. 1994), and was obtained by calculating cross-correlation gain between the power spectral densities of SBP and RR in LF band (0.04–0.15 Hz) by the same method of TFA (La Rovere et al. 2008). In what concerns BRS, whatever the method used, higher values are interpreted as more efficient HR buffer in response to BP fluctuations (La Rovere et al. 2008). It should be noticed that TFA gains of CA and BRS (α-index) have opposite interpretations. In CA, increased gain represents higher transmission of BP oscillations to MFV, so CA is a less efficient filter. In the case of BRS, higher gain (higher α-index) represents higher transmission of BP fluctuations to RR, that is, higher RR response to BP transient oscillations.

Statistics

Normality of the variables was determined by Shapiro–Wilk test. No statistical significant differences were detected between right and left MCA hemodynamic measurements by paired T-test, whereby both MCA values were averaged and used in subsequent analysis. Hemodynamic variables were

compared between sex and age groups in analysis of covariance (ANCOVA) and used Bonferroni post-hoc adjustments for multiple comparisons. The association between cerebral autoregulation and autonomic variables were studied with Spearman's Rho correlations at first. These correlations were adjusted to age group, sex or SBP level with linear regression models. Scatterplots were produced for a better visual representation of those associations. Statistical significance was inferred from $p < 0.05$.

Results

Systemic hemodynamic parameters

Characteristics of the subjects ($n = 95$) differ among age and sex subgroups (see Table 1). Middle- and old-age subjects had increased SBP, MBP and DBP ($p < 0.002$) compared to the young. Older females had SBP and DBP higher compared to males of similar age ($p = 0.001$ and $p = 0.040$). On the other hand, young women showed significantly lower SBP when compared to young males ($p < 0.001$). PP was significantly higher in older versus young subgroups in both sex groups ($p = 0.001$). SBP variability did not differ significantly between age groups or sexes. However, MBP variability at LF band decreased with age when older were compared to the young subgroup ($p = 0.015$).

Cerebrovascular parameters

MFV decreased significantly with age in both sexes (see Table 1: $p < 0.001$). Also, older subjects had higher CVRi and RAP when compared to youngest ($p < 0.001$). Women showed higher MFV values compared to males in middle and young subgroups ($p = 0.002$). Moreover, young women had lower CVRi ($p = 0.038$) and RAP ($p = 0.03$) than males of the similar ages. Older individuals also had lower MFV variability in VLF ($p = 0.028$) and LF range ($p = 0.004$). CA parameters gain and phase did not show significant differences between age or sex subgroups. On the contrary, coherence at LF and HF bands decreased significantly in the older groups compared to the young ($p = 0.030$ and $p = 0.014$).

Baroreflex parameters

BRS decreased with age (xBRS, $p < 0.001$ and α-index, $p < 0.001$). There were no differences between sexes.

Correlation of cerebral autoregulation with BRS

BRS efficacy was inversely related to that of CA, as there was a positive correlation between BRS and CA LF gain (see Tables 2 and 3). It should be noticed that higher BRS means higher BR buffer capacity and that higher gain values means lower dampening capacity of ABP oscillations at brain level, i.e., lower CA capacity. This was true with BRS assessed in time [Table 3: ×BRS multivariate linear regression $\beta = 0.41$ (confidence interval, CI, 95% 0.31; 0.61), $p < 0.001$] as well as in frequency domain [Table 3: α-index, $\beta = 0.56$ (CI95% 0.35; 0.70), $p < 0.001$]. CA HF gain, coherence and phase were not significantly correlated to BRS (see Table 2) when adjusted to cofounders (Online Resource Supplemental table 1 and Table 3).

None of these relationships were different between sexes.

Effects of age and sex on relationships between CA and BRS or SBP variability

CA LF gain correlated significantly with the BR index, xBRS, but not in the older subgroup [see Fig. 1a and Table 3: $\beta = 0.08$ (CI95% −0.41; 0.62), $p = 0.349$]. On the other hand, CA LF gain correlated with SBP level in this older subgroup, [Fig. 1a and Table 3: $\beta = -0.02$ (CI95% −0.03; −0.01), $p = 0.003$] but not young and middle aged. Lastly, CA LF phase showed a positive correlation with LF SBP variability (Table 2 $r = 0.237$, $p < 0.01$), a relationship that was also statistically significant in multivariate regression (Table 3: $R^2 = 11\%$, $p < 0.01$), and which was independent of sex or age subgroups (see Fig. 1e, f).

Discussion

This study characterizes the relationships between CA and BRS in resting conditions and how age and sex modulate this interplay. Our main finding is that ageing modulates the relationship between BR indexes (×BRS and α-index) and CA LF gain of the transfer function of MBP to MFV.

BRS indexes correlate significantly with CA LF gain, meaning that their efficacy is inversely related, but this holds true only for young- and middle-age subjects. In older individuals, CA and BRS are not related to each other. Instead, CA LF gain is dependent on SBP level, with less efficient autoregulation (higher LF gain) associated with lower SBP.

Other important findings are manifold. Firstly, we found that MBP, as well as BRS, was significantly reduced in the old-aged.

Secondly, we documented that CA LF phase is correlated to SBP variability, meaning that the higher the SBP variability the more efficient is CA in buffering ABP oscillations. Nonetheless, it is important to considerate here that ABP spectral power, which can affect both BR gain and TFA estimates (Tzeng et al. 2010; Claassen et al. 2016), could be in part responsible for the relationship between gain and BRS, despite the fact that this was not shown by linear regression analysis (supplemental Table 1).

Table 1 Baseline demographic and hemodynamic characteristics of all participants ($N=95$) and among subgroups of young (≤40 years-old), middle age (41–60 years-old) and older individuals (≥61 years-old) and between sexes

Variable	All	Males ($N=46$)			Females ($N=49$)			ANCOVA			
		Young ($N=20$)	Middle age ($N=14$)	Old ($N=10$)	Young ($N=22$)	Middle age ($N=16$)	Old ($N=11$)	R^2	Age effect	Sex effect	Interaction
Demographic											
Age, years	45 ± 17	30 ± 6	*50 ± 5	*† 72 ± 7	29 ± 6	*49 ± 4	*† 71 ± 5	0.908	< 0.001	0.658	0.756
BMI, kg m^{-2}	25 ± 4	24 ± 3	25 ± 2	27 ± 3	22 ± 6	24 ± 2	25 ± 3	0.122	0.970	0.456	0.348
Systemic hemodynamic											
ABP Systolic, mm Hg	120 ± 18	114 ± 13	*126 ± 13	*†131 ± 11	∫105 ± 16	*124 ± 1	*†∫135 ± 11	0.382	< 0.001	0.002	0.040
Mean	90 ± 14	84 ± 11	*98 ± 8	*95 ± 12	83 ± 15	*93 ± 13	* 99 ± 16	0.324	< 0.001	0.267	0.091
Diastolic	69 ± 14	65 ± 11	*76 ± 16	*72 ± 13	60 ± 12	*72 ± 13	*†∫82 ± 17	0.105	< 0.001	0.034	0.103
Pulse pressure	45 ± 15	43 ± 10	44 ± 11	*†56 ± 15	47 ± 12	*52 ± 11	*† 56 ± 11	0.102	0.030	0.883	0.462
SBP LF, mm Hg^2	6.0 ± 4.1	6.2 ± 5.6	8.4 ± 4.5	7.4 ± 4.8	5.2 ± 4.6	8.4 ± 5.1	4.7 ± 2.6	0.134	0.056	0.087	0.460
HF	3.4 ± 3.2	2.3 ± 1.3	3.4 ± 3.1	5.1 ± 5.2	3.1 ± 2.3	2.4 ± 1.7	5.4 ± 1.1	0.200	0.100	0.137	0.056
MBP LF, mm Hg^2	1.7 ± 2.1	2.2 ± 1.5	2.0 ± 2.5	*1.0 ± 4.8	1.9 ± 1.6	2.2 ± 1.8	*1.2 ± 0.6	0.236	0.020	0.748	0.817
HF	6.0 ± 5.1	0.4 ± 0.3	0.6 ± 0.6	1.4 ± 2.5	0.4 ± 1.3	0.3 ± 1.7	0.7 ± 1.1	0.113	0.057	0.137	0.069
RR, ms	898 ± 129	846 ± 103	951 ± 143	*†1009 ± 165	863 ± 107	879 ± 123	*929 ± 105	0.016	0.001	0.088	0.128
$EtCO_2$, mm Hg	37.3 ± 9.7	37.1 ± 2.0	40.1 ± 7.3	37.9 ± 2.1	35.3 ± 8.4	37.6 ± 6.2	36.1 ± 7.5	0.103	0.077	0.125	0.678
Baroreflex sensitivity											
xBRS, ms/mm Hg^{-1}	11.4 ± 7.3	14.1 ± 8.2	11.5 ± 9.6	*† 6.4 ± 3.5	14.5 ± 6.1	*10.1 ± 5.4	*†5.1 ± 5.9	0.281	< 0.001	0.483	0.643
α-Index, ms/mm Hg^{-1}	8.4 ± 4.9	10.1 ± 4.3	9.2 ± 7.7	*† 4.3 ± 2.1	10.3 ± 5.2	*6.7 ± 3.6	*†3.7 ± 4.8	0.264	< 0.001	0.967	0.278
Cerebral hemodynamics											
CBFV systolic, $cm.s^{-1}$	93 ± 18	93 ± 18	*85 ± 22	*86 ± 18	∫103 ± 16	∫93 ± 15	*85 ± 16	0.226	0.032	0.037	0.458
Mean	67 ± 13	65 ± 13	*61 ± 13	*56 ± 15	∫75 ± 12	*∫68 ± 11	*†58 ± 13	0.150	< 0.001	0.006	0.345
Diastolic	46 ± 10	48 ± 8	*43 ± 10	*† 35 ± 9	∫52 ± 12	*∫49 ± 11	*†37 ± 8	0.230	< 0.001	0.047	0.239
CVRi,mmHg.$cm^{-1}.s^{-2}$	1.2 ± 0.3	1.2 ± 0.3	*1.3 ± 0.4	*1.4 ± 0.3	∫1.0 ± 0.2	*1.3 ± 0.3	*1.5 ± 0.4	0.193	< 0.001	0.015	0.046
RAP,mmHg.$cm^{-1}.s^{-2}$	1.1 ± 0.3	1.0 ± 0.3	*1.3 ± 0.4	*1.3 ± 0.3	∫0.9 ± 0.2	*1.1 ± 0.3	*1.4 ± 0.4	0.256	< 0.001	0.004	0.028
CrCP, mm Hg	13 ± 12	16 ± 18	7 ± 16	14 ± 15	15 ± 12	9 ± 24	18 ± 13	0.186	0.413	0.556	0.847
MFV VLF, $cm^{-1}.s^{-2}$	3.1 ± 3.8	1.9 ± 2.2	1.7 ± 2.7	*1.5 ± 5.3	2.5 ± 5.6	1.8 ± 2.6	*1.2 ± 0.6	0.344	0.030	0.123	0.075
LF	1.9 ± 1.5	1.9 ± 1.4	*1.2 ± 1.3	*0.5 ± 0.4	2.2 ± 2.0	*1.7 ± 1.0	*0.6 ± 0.6	0.233	0.001	0.268	0.485
HF	0.8 ± 0.6	0.8 ± 0.5	0.6 ± 0.4	0.6 ± 1.0	1.1 ± 0.6	0.6 ± 0.4	0.6 ± 0.2	0.132	0.459	0.769	0.079
Cerebral autoregulation											
Phase VLF, radians	1.0 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	0.8 ± 0.5	0.9 ± 0.3	1.1 ± 0.4	0.9 ± 0.3	0.006	0.856	0.748	0.295
LF	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.5	0.7 ± 0.6	0.8 ± 0.4	0.7 ± 0.2	0.6 ± 0.3	0.031	0.417	0.464	0.429
HF	0.1 ± 0.5	0.1 ± 0.5	0 ± 0.5	0.1 ± 0.5	0.1 ± 0.5	0 ± 0.3	0 ± 0.4	0.000	0.598	0.985	0.950
Gain VLF, %.mm Hg^{-1}	1.0 ± 0.4	1.0 ± 0.4	0.9 ± 0.5	1.0 ± 0.4	0.9 ± 0.5	0.9 ± 0.3	0.7 ± 0.2	0.112	0.430	0.430	0.430
LF	1.4 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.189	0.090	0.202	0.294
HF	1.6 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	1.3 ± 0.1	1.8 ± 0.3	1.7 ± 0.2	1.4 ± 0.2	0.189	0.074	0.104	0.394

Table 1 (continued)

Variable	All	Males ($N=46$)			Females ($N=49$)			ANCOVA			
		Young ($N=20$)	Middle age ($N=14$)	Old ($N=10$)	Young ($N=22$)	Middle age ($N=16$)	Old ($N=11$)	R^2	Age effect	Sex effect	Interaction
Coherence VLF, a.u	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.022	0.542	0.873	0.827
LF	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	*0.5 ± 0.2	0.6 ± 0.1	0.7 ± 0.1	*0.5 ± 0.2	0.135	0.014	0.127	0.284
HF	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	*0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	*0.5 ± 0.1	0.086	0.026	0.069	0.104

ms milliseconds, *a.u.* arbitrary units, *BMI* body mass index, $EtCO_2$ end-tidal CO_2, *RR* heart inter-beat interval duration, *MBP* mean blood pressure, *MFV* mean cerebral blood flow velocity, *CVRi* cerebrovascular resistance index, *SD* standard deviation, *SBP* systolic blood pressure, *xBRS* cross-correlation baroreflex sensitivity, *α-index* baroreflex gain in frequency domain. All values are given in mean ± SD. $p<0.05$ significance for ANCOVA differences between young (*) or middle-age (†), and between sexes ($\int$) accordingly to post-hoc Bonferroni procedure. VLF, LF and HF are very-low, low and frequency bands. In systemic hemodynamics LF is 0.04–0.15 Hz; HF is 0.15–0.4 Hz; in cerebral hemodynamics VLF is 0.02–0.07 Hz; LF 0.07–0.2 Hz and HF 0.2–0.5 Hz

Table 2 Correlation (Spearman's Rho coefficients) between cerebral autoregulation and autonomic measurements

	Baroreflex sensitivity		SBP (mm Hg)
	xBRS, $ms.mmHg^{-1}$	α-index, $ms.mmHg^{-1}$	
LF coherence, a.u	0.193	**0.308	− 0.099
HF coherence	0.169	0.197	*− 0.189
LF gain, $\%.mmHg^{-1}$	**0.443	**0.508	**− 0.486
HF gain	**0.399	**0.379	**− 0.547
LF phase, radians	0.001	− 0.045	0.025
HF phase	0.022	0.027	− 0.195

α-Index baroreflex gain in frequency domain, ×*BRS* cross-correlation baroreflex sensitivity. Cerebral autoregulation parameters phase and gain are presented at spectral bands of low- (LF: 0.07–0.20 Hz) and high (HF: 0.2–0.5 Hz)-frequency ranges as suggested by guidelines (Claassen et al. 2016). *$p<0.05$ and **$p<0.01$ significance of Spearman's correlation coefficient

Thirdly, despite the different MFV and ABP steady-state levels between women and males, CA parameters and its interplay with BRS or HRV are not significantly altered by sex.

Taken together, these findings suggest that the interplay between peripheral and central mechanisms, which help to maintain an adequate cerebral flow, suffers changes with age. Cardiac baroreflex works in correlation with CA in the young, but as BRS gradually deteriorates with ageing, SBP steady-state level becomes more relevant to maintain adequate cerebrovascular dampening of the cerebral oscillations. While these correlations do not imply a causal link, when baroreflex is effective it seems to have an association with a lower cerebrovascular dampening capacity. Possibly, as one of the mechanisms is activated, the other is not so necessary to maintain stability, and vice-versa. Tzeng et al. (2010) and Nasr et al. (2014) have already suggested this integrated compensatory relationship, and it is supported by the "cross-talk" hypothesis, presented by Sykora et al. (Sykora et al. 2009). The role of SBP on regulation of CA, which seems greater with age, may reflect a similar mechanism as described on kidney autoregulation (Carlstrom et al. 2015).

Age effects in general hemodynamic parameters

The decrease in MFV and increase in cerebrovascular resistance with ageing, measured by CVRi and RAP, is in agreement with previous studies (Madureira et al. 2017; Xing et al. 2017; Krejza et al. 1999; Bakker et al. 1999). These changes can be explained by various vascular pathological derangements associated with advanced age, such as microvascular rarefaction, vessel tortuosity, venous collagenoses increasing downstream resistance, basement

Table 3 Multiple regression analysis of cerebral autoregulation and autonomic measurements by subgroup of age and sexes

Dependent variables		Independent variables							
LF gain	R2	xBRS, ms.mmHg^{-1}			α-Index, ms.mmHg^{-1}			SBP, mm Hg	
		β (95% CI)	*p* value	R2	β (95% CI)	*p*	R2	β (95% CI)	*p*
All	0.20	0.41 (0.31; 0.61)	< 0.001	0.27	0.56 (0.35; 0.70)	< 0.001	0.16	− 0.01 (− 0.01; − 0.004)	0.002
≤ 40 years	0.26	0.56 (0.31; 0.85)	< 0.001	0.29	0.66 (0.31; 0.85)	< 0.001	0.07	− 0.01 (− 0.02; 0.01)	0.234
41–60 years	0.11	0.31 (0.07; 0.41)	0.040	0.19	0.41 (0.08; 0.74)	0.016	0.11	− 0.01 (− 0.02; 0.01)	0.673
≥ *61 years*	0.01	0.10 (− 0.41; 0.62)	0.349	0.01	0.33 (− 0.21; 0.87)	0.216	0.52	− 0.02 (− 0.03; − 0.02)	0.002
Male	0.37	0.40 (0.11; 0.70)	0.013	0.20	0.49 (0.19; 0.80)	0.002	0.13	− 0.03 (− 0.02; 0.001)	0.092
Female	0.31	0.51 (0.28; 0.74)	< 0.001	0.40	0.56 (0.35; 0.76)	< 0.001	0.22	− 0.02 (− 0.01; − 0.002)	0.044

Multivariate linear regression analysis: when comparing age groups, it was adjusted for sex and SBP; when sexes were compared it was adjusted for age and SBP; when SBP was used as independent variable, only sex or age was used in adjustment

β standardized beta coefficient, *CI* confidence interval, R^2 coefficient of determination, *α-index* baroreflex gain in frequency domain in ms.mm Hg^{-1}, *×BRS*, cross-correlation baroreflex sensitivity in ms.mm Hg^{-1}, *SBP* systolic blood pressure in mm Hg; cerebral autoregulation parameter of gain (%.mm Hg^{-1}) is presented at spectral bands of low (LF: 0.07–0.20 Hz) frequency range as suggested by guidelines (Claassen et al. 2016); α-index and SBP variability analysis were calculated at spectral ranges of low (LF: 0.04–0.15 Hz) and high (HF: 0.15–0.4 Hz) frequency ranges (Westerhof et al. 2004)

membrane thickness and endothelial stripping (Brown and Thore 2011). Moreover, ageing is associated with endothelial dysfunction with vessel wall smooth muscle disorganization and rigidity, which causes impaired vasomotor responses and sustained vasoconstriction (Iadecola 2004). Also, the increase in arterial pulsatility with age supports the notion of a systemic increase in vascular rigidity, which could also contribute to diffuse cerebral microvascular disease (Nation et al. 2015).

Age effects on the mechanisms of vascular regulation

A decline in BR efficacy with ageing was already referred in previous studies (Gribbin et al. 1971). This can be explained by the several structural changes in the vascular tree which occur with ageing, as already described. Moreover, Pierce et al. (2016) recently described the stiffening of the carotid artery as another mechanism predictor of changes on baroreflex sensitivity which occurs with ageing. In opposition, CA measures have not suffered significant changes with age in our study, in accordance with previous studies (Yam et al. 2005; Madureira et al. 2017; Carey et al. 2000). As so, despite a generalized increase in vascular rigidity, the brain vasculature seems to have compensatory adjustments, allowing maintenance of the stability of brain perfusion even in the presence of chronic or slowly progressive baroreflex dysfunction, such as occurs in ageing. This was shown not only for CA but also for neurovascular coupling (Carey et al. 2000; Madureira et al. 2017; Groschel et al. 2007).

Interplay between CA and BRS

BRS correlated significantly with LF gain, meaning that their efficacy is inversely related. Others (Tzeng et al. 2010; Nasr et al. 2014) have already reported this inverse correlation with other methods but they studied only young healthy subjects. Our study confirms that there is a positive correlation between BR measures and CA LF gain but provides additional interesting new findings. We expand this knowledge by showing that this tight relationship is lost with ageing. Contrary to younger subjects, older individuals do not show a correlation between CA LF gain and BR indexes. Instead, in old-aged subjects, CA LF gain is better explained by SBP steady-state level—the lower the SBP, the less efficient CA is in dampening ABP oscillations (higher LF gain)—with the note, as previously, of the effect of variation of ABP on estimates of gain and phase (Tzeng et al. 2010). This correlation between SBP and CA LF gain was not present at young ages. Our data suggest that in older individuals with a reduced BP, compared to other groups, BP fluctuations are less efficiently counteracted at the cerebrovascular level. This may explain why older subjects are more susceptible to transient reduction of cerebral blood flow (more postural symptoms, syncope, cerebral ischemia, etc.) or its sudden increment (anti-hypertensive drugs withdrawal, hypertensive crises, cerebral haemorrhage, etc.). A diminished BR and the need to maintain a balanced CA, which improves dependent on higher steady-state values of SBP, may explain the reason why the treatment of arterial hypertension in the elderly should be cautious, to not interfere with this balance. The SBP reference cut-off value of 140 mm Hg to medical intervention used in general population is replaced by

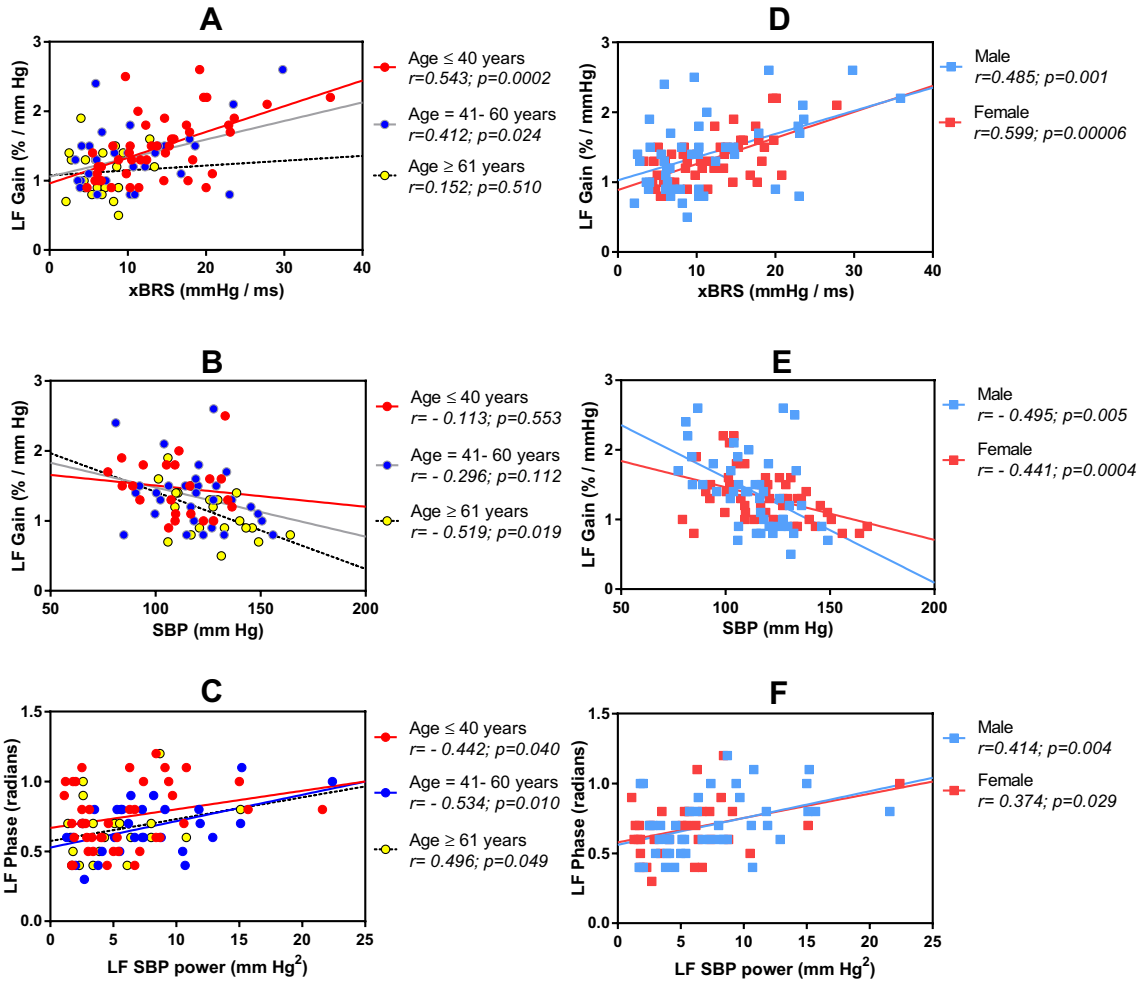

Fig. 1 Scatter plots showing the interplay between indices of cerebral autoregulation and autonomic measures stratified by age subgroups of young (age ≤ 40 years-old), middle age (41–60 years-old) and older subgroups (age ≥ 61 years-old) and between sexes. The Spearman's correlation coefficients and level of significance of each subgroup are shown at right top corner. **a, b** Represent the relationship between CA LF gain with xBRS (baroreflex sensitivity) between age and sex groups, respectively. **c, d** Represent the relationship between CA LF gain and SBP level in among age subgroups and between sexes, respectively. **e, f** Represent the relationship between CA phase with SBP variability in LF band among age subgroups and between sexes, respectively. *CA* cerebral autoregulation, *LF* low-frequency spectral band (CA is 0.07–0.20 and for xBRS 0.04–0.15 Hz), *SBP* systolic blood pressure, ×*BRS* cross-correlation baroreflex sensitivity

150 mm Hg in this group population (Mancia et al. 2009) since studies have shown an increased mortality risk with a more aggressive treatment for hypertension in elderly (Zanchetti et al. 2009).

A word of caution should be taken by the fact that gain is just one of the various parameters that reflex CA. It represents the dampening capacity of cerebral vessels in face of ABP oscillations. So this correlation might not be synonym of an inverse relationship between CA and BR efficacy in a wider sense. The parameter phase was found to be the most robust measure to evaluate CA (Tzeng et al. 2012), yet there is a lack of an accepted gold standard. There is also evidence that gain and phase represent different aspects of cerebrovascular regulation. For example, a reduced phase has been related to larger cerebral infarction (Castro et al. 2017), and ischemic complications in subarachnoid haemorrhage (Otite et al. 2014) and intracranial haemorrhage (Ma et al. 2016); while LF gain was related with the risk of haemorrhagic transformation (Castro et al. 2017a, b, c) and vasospasm (Otite et al. 2014). Theoretically, gain refers to the amplitude of transmission of MBP to MFV whereas phase is related to the speed of the response to a MBP transient. Regarding the present study, the significant correlations involving CA with BR are mostly relative to CA LF gain measures. Nonetheless, Tzeng et al. (2012) showed the inverse relationship between CA and BR with LF phase and with autoregulatory indexes derived by the thigh-cuff test.

Systolic blood pressure influence in CA efficacy

The positive correlation stated between CA LF phase and LF SBP variability means that a more efficient CA associates with higher SBP variability. We are unaware of any study reporting this finding. Traditionally, LF SBP has been proposed as a surrogate of sympathetic vascular tonus in autonomic failure (Freitas et al. 2007), although this is not concordant with microneurography and catecholamine studies in healthy young and older subjects (Hart et al. 2009). The only studies relating SBP and autoregulation are in kidney circulation (Loutzenhiser et al. 2006). It is interesting to notice that higher SBP and pulsatile flow at the afferent arteriole oscillations act like a "tuner" of the buffering capability of arterial renal flow to ABP fluctuations (Loutzenhiser et al. 2006), i.e., increased SBP enhances renal autoregulation. We can only hypothesize that the same can happen at brain level although more studies are needed to confirm this finding.

Effects on cerebral vasculature related with sex subgroups

In our work, we did find younger women to have higher MFV and lower cerebrovascular resistance (CVR and RAP) than males, a difference that disappeared with increasing age which agrees with previous observations (Kastrup et al. 1997; Madureira et al. 2017). Also, younger women had lower ABP but this sex difference seems to have inverted in the old subgroup. The ABP sex-related differences have been studied and concluded to be partially driven by estrogens effects on the autonomic nervous system (Hart et al. 2009). Some authors claim that young females have less robust sympathetic vasoconstrictor response (Baker et al. 2016) and predominantly vasodilatory β-agonist activity (Hart et al. 2009), which is partially modulated by sex hormones. Other contributions to this decreased vessel wall tone may be an increased nitric oxide bioavailability in females (Faraci and Brian 1994). Our work adds that what happens in peripheral arteries may also apply to the cerebrovascular bed. A new and especially interesting finding resulted from the study of the dual parameter model of cerebrovascular tonus of RAP + CCP. RAP is mostly of myogenic in nature (Castro et al. 2014, 2017), whereas CCP is influenced by metabolic inputs, like CO_2 (Panerai et al. 1999), neuronal activation (Panerai et al. 2005) and intracranial pressure (Castro et al. 2014). The fact that we did find changes in RAP and not CCP is in line with the hypothesis that younger women have a reduced vascular myogenic tone. Despite these sex-related differences, our data show that sex does not affect CA parameters or the interplay between BRS and CA measures. This means that cerebral blood flow regulation is efficiently controlled in both sexes, although younger women have higher cerebral blood flow and lower cerebrovascular resistance. These results are important since the interference of sex in BRS and CA regulation is scarcely studied in the literature, with previous studies having pooled both male and female subjects (Tzeng et al. 2010).

Limitations

There are several limitations that should be discussed. The study population was screened to exclude cardio- and cerebrovascular risk factors or diseases that may confound the ageing effect. While this strengthens our results, the intentional absence of common vascular risk factors in our study could have diminished the applicability of our results to the general population. Also, some participants had mild dyslipidemia and were on pharmacological control with statins; however, carotid atherosclerosis was excluded by cervical ultrasound study. Based on this cross-sectional study, we cannot determine the causality of the relationships that we have found. Also, the small sample may account for a lower statistical power in this study. These findings should be confirmed in larger multicentre datasets to increase their reliability.

Some caution should be taken when interpreting our results since alpha-index as well as TFA parameters are just indexes that have been adopted to reflect BRS and CA, respectively, but they are not synonymous hence not interchangeable.

Conclusions

Overall, our data suggest that ageing is characterized by a loss of balance between arterial baroreflex measures and the cerebral autoregulation parameter LF gain, while there is no major effect of sex.

A more active cerebral autoregulation is associated with a less efficient arterial baroreflex and vice-versa, but this relationship is only kept at younger ages. In the older, who present a reduced baroreflex efficacy, steady-state blood pressure level is particularly important for cerebrovascular regulation.

Author contributions ST, JM, EA and PC conceived and designed research. JM and PC conducted experiments. ST and PC analysed data. ST and PC wrote the manuscript, EA conveyed critical analysis of the results All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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