The Leicester Cerebral Haemodynamics Database: Normative Values and the Influence of Age and Sex

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Running Headline

Leicester Cerebral Haemodynamics Database

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Abstract

Normative values of physiological parameters hold significance in modern day clinical decision-making. Lack of such normative values has been a major hurdle in the translation of research into clinical practice. A large database containing uniform recordings was constructed to allow more robust estimates of normative ranges and also assess the influence of age and sex.

Doppler recordings were performed on healthy volunteers in the same laboratory, using similar protocols and equipment. Beat-to-beat blood pressure, heart-rate, electrocardiogram, and end-tidal CO_2 were measured continuously. Bilateral insonation of the middle cerebral arteries (MCAs) was performed using TCD following a 15-minute stabilisation, and a 5-minute baseline recording.

Good quality Doppler recordings for both MCAs were obtained in 129 participants (57 female) with a median age of 57 years (range 20-82). Age was found to influence baseline haemodynamic and transfer function analysis parameters. Cerebral blood flow velocity and critical closing pressure were the only sex-related differences found, which was significantly higher in females than males.

Normative values for cerebral haemodynamic parameters have been defined in a large, healthy population. Such age/sex-defined normal values can be used to reduce the burden of collecting additional control data in future studies, as well as to identify disease-associated changes.

Key words

Cerebral haemodynamics, cerebral autoregulation, ageing, sex differences, cerebral blood flow

Abbreviations list

ARI	Cerebral autoregulation index
BP	Blood pressure
CA	Cerebral autoregulation
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CO_2	Carbon dioxide
CrCP	Critical closing pressure
ECG	Electrocardiogram
$EtCO_2$	End-tidal CO2
HF	High frequency
HR	Heart rate
IQR	Inter-quartile range
LF	Low frequency
MBP	Mean blood pressure
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
RAP	Resistance-area product
SD	Standard deviation
TCD	Transcranial Doppler
TFA	Transfer function analysis
VLF	Very-low frequency

Introduction

Clinical decision-making often requires knowledge of normal ranges of physiological parameters, the diagnosis of hypertension being a classical example. The lack of such normative values for the cerebral circulation has been a major hurdle in the translation of research into clinical practice, particularly with respect to the management of physiological perturbations in the context of hyperacute and acute ischaemic and haemorrhagic stroke. Despite significant advances in our ability to probe the cerebral circulation with non-invasive techniques such as transcranial Doppler ultrasound (TCD), near infrared spectroscopy (NIRS) and magnetic resonance imaging (MRI), there is still a dearth of information regarding the normal ranges of parameters derived from these methods. Due to its relatively low-cost, portability and exceptional temporal resolution, TCD has been the main tool in studies of cerebral haemodynamics. Since its introduction, normative values of cerebral blood flow velocity (CBFV), which correlates well with changes in absolute CBF, have been reported (Adams et al. 1992, Bakker et al. 2004). However, in contrast to other physiological systems, direct measurements of CBFV or related parameters, such as the Pulsatility Index (Adams et al. 1992), do not provide the discriminatory power required to detect abnormalities of the cerebral circulation. Due to the highly effective control exerted by the mechanism of pressure-autoregulation, CBF is normally maintained within narrow limits for mean blood pressures (MBP) in the range 60-150 mm Hg (Paulson, Strandgaard & Edvinsson 1990). Not surprisingly, it is the CBF autoregulation mechanism itself that has been shown to be impaired in a number of conditions such as ischaemic stroke, severe head injury, carotid artery disease, intracranial hypertension, diabetes and liver failure (Aries et al. 2010, Czosnyka et al. 1996, Dawson et al. 2000, Hauerberg, Juhler 1994, Kim et al. 2008, Lagi et al. 2002, Panerai 2008, White, Markus 1997, van Beek et al. 2008).

Most clinical studies of cerebral autoregulation (CA) have used transfer function analysis based on spontaneous fluctuations of MBP and CBFV, using amplitude (gain) and phase frequency responses as markers of the effectiveness of CA (Panerai et al. 1998a, Zhang et al. 1998). The autoregulation index (ARI) proposed by Tiecks *et al* (Tiecks et al. 1995), usually obtained from thigh cuff manoeuvres (Tiecks et al. 1995, Aaslid et al. 1989), can also be derived by TFA (Panerai et al. 1998b) and together with phase has been shown to be the most sensitive parameter to detect abnormalities in CBF regulation (Panerai 2008). Both the ARI and phase have been shown to have satisfactory, but not outstanding, reproducibility (Birch, Neil-Dwyer & Murrills 2002, Brodie et al. 2009, Gommer et al. 2010). Despite these encouraging studies, normative values of ARI and phase have not been reported for two main reasons. Firstly, most studies have enrolled a relatively small number of subjects which sets limits on the statistical reliability of results. Secondly, it has been nearly impossible to pool together different studies to increase the statistical power of estimates due to the considerable diversity of methods used by different centres (Meel-van den Abeelen et al. 2014b). The recent proposal to improve standardisation of these methods (Claassen et al. 2016, Meel-van den Abeelen et al. 2014a), should bear fruit in the near future, but in the meantime alternative approaches are needed. To address these two main limitations, the Department of Cardiovascular Sciences, University of Leicester, UK, has constructed a large database incorporating recordings from a series of separate studies that were all performed in the same laboratory, using similar protocols and equipment. Using this new resource, we have extracted normative values of ARI and phase, which are the main parameters of clinical interest (Panerai 2008), and have also, tested the hypotheses that these parameters are not influenced by age and sex. These hypotheses were tested following previous observations showing effect of age and sex on CA and CBFV (Vriens et al. 1989, Marinoni et al. 1998). For the sake of completeness, and to share information with the scientific community about

parameters that might be of interest for future studies, we have also reported on normative values of other parameters such as critical closing pressure, resistance-area product, coherence, gain and spectral powers.

Methods

Subjects and measurements

Healthy volunteers were recruited from departmental staff and their relatives and provided informed consent in compliance with local ethics committee approvals for all previous studies (Brodie et al. 2009, Haunton 2013, Katsogridakis et al. 2013, Saeed et al. 2013, Salinet, Panerai & Robinson 2014, Minhas et al. 2016). Exclusion criteria included poor insonation of both temporal bone windows and any history of cardiovascular, neurological, or respiratory disease. Volunteers avoided caffeine, alcohol, and nicotine for ≥4 h before attending a research laboratory with controlled temperature (20-23°C) and free from visual or auditory stimulation. Beat-to-beat blood pressure (BP) was recorded continuously using the Finapres or Finometer devices (FMS, Finapres Measurement Systems, Arnhem, Netherlands), attached to the middle finger of the dominant hand. Both devices use the principle of arterial volume clamping of the digital artery and are considered interchangeable. The servo-correcting mechanism of the Finometer was switched on and then off prior to measurements. Heart rate (HR) interval was recorded using a 3-lead electrocardiogram (ECG) and end-tidal CO_2 ($EtCO_2$) was measured via nasal prongs (Salter Labs) by a capnograph (Capnocheck Plus). Bilateral insonation of the middle cerebral arteries (MCAs) was performed using TCD (Viasys Companion III; Viasys Healthcare) with a 2 MHz probe, which was secured in place using a head-frame. During the entire procedure, subjects were in a supine position and detailed instructions were given before taking measurements.

Participants' systolic and diastolic BP were measured by classical brachial sphygmomanometry followed by a period of 15-min stabilisation and a 5-min baseline recording.

Data analysis

Data were simultaneously recorded onto a data acquisition system (PHYSIDAS, Department of Medical Physics, University Hospitals of Leicester) for subsequent off-line analysis using a sampling rate of 500 samples/s and BP was calibrated at the start of each recording. All signals were visually inspected to identify artefacts; noise and narrow spikes (<100 ms) were removed by linear interpolation. CBFV channels were subjected to a median filter and all signals were low-pass filtered with a cut-off frequency of 20 Hz. The R–R interval was then automatically marked from the ECG and continuous HR plotted against time. Occasional missed marks caused spikes in the HR signal; these were manually removed by remarking the R–R intervals for the time points at which they occurred. Mean BP and CBFV values were calculated for each cardiac cycle. The end of each expiratory phase was detected in the $EtCO_2$ signal, linearly interpolated, and resampled with each cardiac cycle. Beat-to-beat data were spline interpolated and resampled at 5 samples/s to produce signals with a uniform time-base. Parameter values were excluded from further analysis using the following limits to define outliers: CBFV (<30 cm/s), $EtCO_2$ (<25 mmHg), HR (<40 bpm), CrCP (<0 mmHg), MBP (<50 mmHg) and resistance-area product (RAP) (>5 mm Hg.s/cm). These thresholds represent extreme values that are not expected to occur in healthy subjects.

Transfer function analysis of the BP-CBFV relationship was performed using Welch's method. The 5-min recording was broken down into segments with 102.4 s duration. The mean value was removed and a cosine window was applied to minimise spectral leakage.

With 50% superposition of segments, usually five segments of data were used to obtain estimates of the BP and CBFV auto-spectra using the fast Fourier transform (FFT) and also the cross-spectra of these two quantities. Using standard procedures (Panerai et al. 1998a, Zhang et al. 1998, Panerai et al. 1998b, Gommer et al. 2010, Meel-van den Abeelen et al. 2014b, Katsogridakis et al. 2013), the coherence function, amplitude (gain) and phase frequency responses were calculated from the auto- and cross-spectra. The coherence function was visually inspected and TFA estimates were only accepted if the coherence was above 0.5 in the frequency range 0.15-0.25Hz where the BP-CBFV relationship can be assumed to be linear (Claassen et al. 2016). These parameters were then averaged for the very-low frequency (VLF, 0.02-0.10 Hz), low frequency (LF, 0.10-0.25 Hz) and high frequency (0.25-0.40 Hz) bands.

The autoregulation index (ARI), which represents dynamic CA, was extracted by using the best least-squares fit between the CBFV step response and one of the 10 model ARI curves proposed by Tiecks et al. (1995) (Panerai et al. 1998b, Tiecks et al. 1995). The ARI was computed for each subject separately for left and right hemispheres for each recording.

Statistical analysis

Statistical analyses were performed using a statistical software package (SPSS, version 20.0; SPSS Inc). Tests for normality were performed using the Kolmogorov–Smirnov test. Data are presented as median and interquartile range (25^{th}-75^{th} percentile) unless stated otherwise. Mean values of each variable were calculated from the entire 5-min baseline recording. Differences in variables were assessed using a Student's *t*-test and Mann-Whitney U test as appropriate. Association between variables were tested using linear regression correlation coefficient or Spearman's rank test as appropriate. Differences between values derived for the

right and left hemispheres were assessed with the paired Student's *t*-test or the Wilcoxon test and were averaged when no significant differences were found. A *p*-value of < 0.05 was assumed to indicate statistical significance.

Results

Data were collected for 180 participants. Redundant recordings from departmental staff participating in more than one study were removed (n=28), as well as recordings that contained only one-sided CBFV (n=13). Ten recordings were excluded due to the outlier criteria described in Methods. Therefore, good quality Doppler recordings for both MCAs were obtained in 129 participants (57 female) with a median age of 57 years (range 20-82), and used in subsequent analyses. Baseline characteristics obtained for the population studied are summarised in Table 1. None of the parameters studied showed differences between hemispheres, all values reported correspond to the mean for right and left sides. Population average values for coherence, amplitude (gain) and phase frequency responses, as well as input and output powers, are summarised in Table 2. In keeping with baseline characteristics and coherence, amplitude and phase responses, ARI was found not to follow a Gaussian distribution (p=0.02) (Fig. 1, Table 2).

With the exception of CBFV and CrCP, sex had no effect on any of the investigated parameters (Table 3). Median ARI was non-significantly higher in females (5.9 [4.2-6.4] vs. 5.3 [4.5-6.4]).

The influence of age was tested by means of linear regression analysis or Spearman correlation coefficient for all parameters. Significant correlations with age were observed with CBFV, BP, $EtCO_2$, HR, CrCP, Coherence (LF) and Gain (LF), but not ARI or phase

(Table 4). The linear dependence of CBFV with age is illustrated in Fig. 2, which also includes the influence of sex.

Discussion

Normative values

When pooling results from a series of previous studies performed with similar equipment and data collection protocols, we found that main cerebral haemodynamic parameters, as well as parameters often adopted to assess dynamic CA by means of TFA, did not show a Gaussian distribution (Tables 1 & 2). This finding indicates that unless a normal distribution is demonstrated to be the case, non-parametric tests should be adopted when performing statistical analysis of these parameters. The wide literature on dynamic CA (dCA) indicates that TFA phase and ARI are the most sensitive and reliable parameters to detect CA impairment (Panerai 2008). Multi-centre differences in parameter values, and their elevated inter-subject variability, have been major hurdles to identify limits of normality that could be used in clinical practice. Given the relevance of CA in protecting the brain from large fluctuations in BP, it is sensible to propose that emphasis be placed on sensitivity, in detriment of specificity. With this in mind, a 5% confidence limit would suggest that ARI = 3 could be adopted as a threshold of abnormality. For thigh cuff manoeuvres, Tiecks et al (Tiecks et al. 1995) suggested that ARI = 5 should be considered the normal value for healthy subjects. However, given the shape of the distribution curve we obtained for a much larger number of individuals, based on supine baseline recordings at rest (Fig. 1), a threshold of ARI < 4 could still be considered appropriate in situations where investigators want to favour sensitivity, in detriment of specificity, to identify patients that might be at risk of secondary damage due to weakening of CA. This threshold correlates well with studies that have reported abnormality of dCA in patients with severe head injury (Panerai et al. 2004), carotid

artery disease (Panerai et al. 1998b), stroke (Salinet, Panerai & Robinson 2014, Saeed et al. 2013), high altitude depression of CA (Subudhi et al. 2014) and other conditions (Panerai 2008).

For VLF phase, the 5% lower confidence limit would correspond to 0.5 radians (28.6 degrees) as the threshold for abnormality. This limit correlates well with several studies reporting values of VLF phase in cerebrovascular conditions (Panerai 2008, Chen et al. 2014, Immink et al. 2005, Reinhard et al. 2003). In particular, Reinhard et al. (Reinhard et al. 2008) proposed a threshold of normality of 20.6 degrees (0.36 radians), based on analysis of 79 older subjects. Again, the limit of normality indicated by our population, of significantly lower age, would lead to higher values of sensitivity, thus reducing the probability of missing patients at a high risk of secondary damage.

One interesting result of the study is the relatively similar values of coherence obtained for the VLF, LF and HF frequency bands. Previous studies reported lower values of coherence in the VLF band, compared to the LF and HF intervals, which led some investigators to suggest that VLF coherence could be used as a marker of dynamic CA efficiency. Our finding supports previous reviews of the literature (10) showing that VLF coherence does not cluster around values much lower than 0.5 in healthy subjects and thus it is unlikely to have discriminatory power for assessment of CA in clinical applications.

Influence of sex

Several investigators have previously described sex-related differences in CBF in humans (Grolimund, Seiler 1988, Vriens et al. 1989, Marinoni et al. 1998, Muller, Schimrigk 1994, Krejza et al. 1999, Deegan et al. 2009), although in most cases, the number of subjects tended

to be relatively small and only a few studies reported on CBFV (Deegan et al. 2009). Most studies report higher mean blood flow velocities in females over males; however it is questioned whether this difference is limited to specific ages (Vriens et al. 1989, Krejza et al. 1999). Our findings support sex-related differences in cerebral haemodynamics where we report that females have higher CBFV compared to males and lower CrCP. The difference in blood flow velocities between female and male subjects could be explained by differences in the diameter of the MCA, but, on the other hand, the lower value of CrCP could suggest that there is greater vasoconstriction at rest in males (42). Smaller vessel diameter would lead to a higher blood flow velocity in female participants; however studies investigating this phenomenon have shown conflicting results. Müller et al. (Muller et al. 1991), reported that males had a 9.3% larger MCA diameter than female participants. On the other hand, Tarasow et al. (Tarasow et al. 2007), reported larger MCA diameters in males but the difference was not statistically significant. MCA diameters were not measured as part of this study therefore we cannot confirm this theory. The observation that CrCP is also sex-dependent, contrary to RAP (Table 4), provides indirect evidence for the MCA diameter hypothesis, since narrower vessels would collapse at a smaller transmural pressure than wider vessels (Panerai 2003). Another possible explanation for the increased CBFV among females may be the difference in hormonal status compared to men. This is supported by a study that found significantly higher CBF in premenopausal women compared to age-matched men(Rodriguez et al. 1988).

The literature on the influence of sex on dynamic CA parameters is fairly limited, with most studies showing the absence of differences due to sex. One exception is the report of Deegan et al. (Deegan et al. 2009), suggesting that older women have a more efficient CA than men, albeit limited to the posterior cerebral artery, and not the MCA.

The finding that dynamic CA parameters are not influenced by sex has implications for the design of clinical trials. Although the effects of sex need to be confirmed in a larger number of elderly subjects, and in patients with different clinical conditions, the results obtained for healthy individuals suggest that control groups do not need to be split according to sex, thus simplifying the design and cost of clinical studies.

Influence of age

Also confirming a series of earlier studies (Carey et al. 2000), we have not found an association between either ARI or phase with age. Although two other parameters derived from TFA showed an association with age (LF coherence and LF gain, Table 4), this does not imply that dynamic CA is age dependent since these parameters lack consistency to express dynamic CA effectiveness (Panerai 2008, van Beek et al. 2008). The observation that RAP is not influenced by age either, is also noteworthy since changes in RAP have been associated with the myogenic control of small blood vessels as one of the main mechanisms responsible for an active CA (Panerai et al. 2005). On the other hand our results agree with the well-known increase in BP and HR with age and previously reported reductions in CBFV and $EtCO_2$ in older subjects (Mancia et al. 1980, Verbree et al. 2014). Taken together, these results suggest that estimates of ARI, phase or RAP do not need to be corrected for age. It is also important to be aware that CBFV, $EtCO_2$, CrCP and LF coherence do change with ageing when interpreting results from TFA. Above all, it is well known that $PaCO_2$ is a potent determinant of CBF and also affects dynamic CA (Paulson, Strandgaard & Edvinsson 1990, Aaslid et al. 1989, Katsogridakis et al. 2013, Minhas et al. 2016, Marinoni et al. 1998). Therefore, when interpreting estimates of dynamic CA, involving diverse age groups, it is necessary to keep in mind that differences in CA effectiveness might be caused by age-related effects on $EtCO_2$. This observation in fact raises an interesting hypothesis about the

interplay between ageing, $PaCO_2$ and ARI (or phase): it is possible that the decrease in $PaCO_2$ with ageing is masking a small reduction in CA effectiveness with ageing, since hypocapnia tends to improve CA.

The decrease in LF coherence with ageing also has practical consequences. The main use of coherence in studies based on TFA is to determine the statistical significance of the BP-CBF relationship and hence accept or reject estimates of gain, phase and ARI derived from such analyses (Claassen et al. 2016). Specific criteria have been proposed for accepting TFA parameters based on values of coherence (Claassen et al. 2016), but the influence of ageing on these criteria has not been taken into account. If older patients have a greater probability of being rejected from studies due to a reduction in LF coherence, this could lead to bias and distorted results in clinical trials.

Limitations of the study

Measurements of CBFV with TCD can only reflect changes in CBF if the diameter of the MCA remains constant. This assumption is normally acceptable for recordings at rest, as long as $PaCO_2$ remains approximately constant during measurements, as was the case of all studies incorporated into the database (Serrador et al. 2000). Although all these studies were performed in the same research laboratory, and adopted similar protocols and equipment, there were different TCD operators, which might have contributed to a wider distribution of CBFV values and related parameters. An additional limitation of our data was that there was no control over what time of the day recordings were obtained. Further work is needed to confirm a single study by Ainslie et al (Ainslie et al. 2007). reporting an early morning reduction in CA in 20 individuals with decrease in endothelium-dependent vascular reactivity. Although all operators were trained to the same standards and criteria to ensure

that the MCA was being insonated, it is possible that in some cases the insonated vessel was the PCA, leading to smaller CBFV values and for this reason we have treated all values below 30 cm/s as outliers. Fortunately, the main parameters usually adopted to assess the effectiveness of dynamic CA, namely ARI and phase, are not dependent on the amplitude of the BP or CBFV signal, only on the temporal pattern of their relationship.

Further studies might also benefit from a larger number of older subjects. Although the database includes subjects over a wide age range, only 6 subjects were older than 75 years of age. With continuing increases in life expectancy and associated rise in the age-related co-morbidity, such as Alzheimer's and vascular dementia, it is important that this group of subjects is proportionally represented in the database.

Clinical studies investigating CA have used TFA grounded on spontaneous fluctuations of MBP and CBFV with the use of amplitude and phase frequency responses as markers for the efficacy of CA. Frequency domain parameters and ARI, derived from TFA, have shown to be sensitive to physiological changes in patients with a variety of diseases. It is important to note that in addition to TFA, alternative methods have been used to assess the relationship between CBFV and BP such as multimodal pressure flow analysis which may be more resilient to unstable variation in BP and/or CBFV (Czosnyka et al. 1996, Dawson et al. 2000, Panerai 2008, Zhang et al. 1998, Birch, Neil-Dwyer & Murrills 2002, Mitsis et al. 2006). A relationship has been established between impaired CA and clinical outcome, such as traumatic brain injury, cerebral ischaemia, occlusive carotid disease and Alzheimer's disease. Previous data have also demonstrated impairment of CA after subarachnoid haemorrhage. Although these studies demonstrated impairment of CA, comparability between the disease populations to healthy controls has been difficult due to small numbers of participants.

Conclusion

Despite the significant interest and urgent need to bring autoregulation testing into everyday clinical practice to inform the management of physiological perturbations in stroke disease, the overall heterogeneity amongst studies with differing methodologies has not allowed formulation of accurate normative values for cerebral haemodynamic measurements. Here we have presented normative values for over 100 healthy participants which would help distinguish between normal and abnormal CA. Additionally, these guidelines for the interpretation of CA indices and other cerebral haemodynamic parameters will make it possible to assess and monitor patients in a standard manner. We propose that these normative values may be useful to identify patients at risk of cerebral damage that will influence their medical and/ or surgical management.

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Author contribution statement

N Patel carried out the data analysis. V Haunton, E Katsogridakis, N Saeed, A Salinet, N Syed and F Brodie contributed towards data collection. S D'Sa performed data entry and organised the database. R Panerai and T Robinson conceptualised and supervised the studies contributing with data. N Patel, R Panerai and T Robinson drafted the paper. All authors checked and approved the final version of the manuscript.

Disclosure/Conflict of Interest

The authors declare that they have no conflict of interest.

Data Access statement

Due to Ethical Committee requirements for specific patient consent, preceding the recent Research Councils UK directive towards making support data publicly available, it is not possible to make the support data for this study openly accessible.

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Figure legends

Figure 1

Histogram showing the distribution of the ARI values for 129 healthy subjects. Median [IQR: 25^{th}-75^{th} percentile] 5.6 [4.4-6.4], mean (SD) 5.3 (1.5).

Figure 2

CBFV values reported against age in males (●) (linear R (solid line) = 0.344) and females (x) (linear R (dashed line) = 0.389) correlated significantly with age (p=0.000). Average CBFV values were higher in females (median [IQR]) (53.6 [46.9-67.1]) than males (49.9 [43.3-57.1]) (p=0.006).

TABLES

Table 1. Demographic and baseline physiological parameters

	n	Median (IQR)	Mean (SD)	*p*-value (KS test)
Age (years)	129	57.0 (42.5-67.0)	53.6 (15.8)	0.008
CBFV (cm s^{-1})	129	51.1 (44.7-59.7)	52.8 (12.4)	NS
Mean Arterial BP (mm Hg)	129	89.7 (80.6-96.2)	88.3 (12.5)	0.002
End-tidal CO_2 (%)	119	39.1 (36.9-40.8)	38.6 (3.9)	0.003
Heart rate (beats/min)	126	64.6 (59.0-70.0)	64.4 (9.6)	NS
CrCP (mm Hg)	121	27.7 (17.4-40.1)	28.6 (15.4)	NS
RAP (mm Hg cm s^{-1})	129	1.21 (1.0-1.5)	1.32 (0.5)	0.018

n, number of participants (see Methods for exclusion criteria); IQR, inter-quartile range (25^{th} – 75^{th} percentile); SD, standard deviation; KS, Kolmogorov-Smirnov test; NS, non-significant; CBFV, cerebral blood flow velocity; BP, blood pressure; CrCP, critical closing pressure; RAP, resistance-area product.

Table 2. Distribution values of the autoregulation index (ARI) and transfer function analysis parameters

	Median (IQR)	Mean (SD)	*p*-value (KS test)
Coherence VLF range	0.5 (0.4-0.6)	0.5 (0.1)	0.015
Coherence LF range	0.7 (0.6-0.8)	0.6 (0.1)	0.001
Coherence HF range	0.5 (0.4-0.7)	0.6 (0.2)	NS
Gain VLF range (cm s^{-1} mm Hg^{-1})	0.6 (0.5-0.8)	0.7 (0.3)	0.000
Gain LF range (cm s^{-1} mm Hg^{-1})	0.9 (0.7-1.2)	1.0 (0.5)	0.000
Gain HF range (cm s^{-1} mm Hg^{-1})	1.0 (0.8-1.2)	1.0 (0.4)	0.015
Phase VLF range (radians)	0.8 (0.6-1.0)	0.8 (0.4)	NS
Phase LF range (radians)	0.5 (0.3-0.6)	0.5 (0.2)	0.040
Phase HF range (radians)	-0.02 (-1.2-0.1)	-0.009 (0.3)	0.000
BP power VLF range $(mmHg)^2$	15.3 (10.6-25.2)	21.6 (18.4)	0.000
BP power LF range $(mmHg)^2$	1.7 (1.0-2.8)	2.9 (3.79)	0.000
BP power HF range $(mmHg)^2$	0.3 (0.15-0.57)	0.5 (0.7)	0.000
CBFV power VLF range (cm $s^{-1})^2$	21.7 (11.1-32.6)	25.6 (19.2)	0.000
CBFV power LF range (cm $s^{-1})^2$	1.5 (0.8-3.0)	2.8 (4.6)	0.000
CBFV power HF range (cm $s^{-1})^2$	0.2 (0.1-0.4)	0.3 (0.4)	0.000
ARI	5.6 (4.4-6.4)	5.3 (1.5)	0.020

IQR, Inter-quartile range (25^{th} – 75^{th} percentile); SD, standard deviation; KS, Kolmogorov-Smirnov test; NS, non-significant; VLF, Very low frequency; LF, Low frequency; HF, High frequency; CBFV, cerebral blood flow velocity; BP, blood pressure; ARI, Cerebral autoregulation index.

Table 3. Influence of sex on baseline physiological parameters and ARI

	Male		Female		
	n	**Median (IQR)**	***n***	**Median (IQR)**	***p*-value**
Age (years)	72	57.0 (46.0-67.0)	57	52.0 (38.0-66.6)	0.566*
CBFV (cm s^{-1})	72	49.9 (43.3-57.1)	57	53.6 (46.9-67.1)	0.006†
Mean Arterial BP (mm Hg)	72	89.7 (82.7-98.9)	57	89.9 (77.4-94.7)	0.291*
End-tidal CO_2 (%)	67	39.3 (36.6-40.7)	52	39.0 (37.1-40.9)	0.690*
Heart rate (beats/min)	70	64.4 (59.3-69.6)	56	65.5 (58.4-72.6)	0.521†
CrCP (mm Hg)	66	31.2 (18.3-41.8)	55	24.2 (13.6-38.9)	0.044†
RAP (mm Hg cm s^{-1})	72	1.32 (1.0-1.5)	57	1.13 (0.9-1.4)	0.070*
ARI	72	5.3 (4.5-6.4)	57	5.9 (4.2-6.4)	0.480*

n, number of participants (see Methods for exclusion criteria); IQR, inter-quartile range (25^{th} – 75^{th} percentile); CBFV, cerebral blood flow velocity; BP, blood pressure; CrCP, critical closing pressure; RAP, resistance-area product; ARI, Cerebral autoregulation index; *, Mann-Whitney U test; †, *t*-test.

Table 4. Influence of age on main physiological and transfer function analysis parameters. Only parameters showing significant association with age are listed.

	n	**CC**	**Regression coefficients**	**p-value**
CBFV (cm s^{-1})	129	0.247	63.2 -0.19*AGE	0.005
Mean Arterial BP (mm Hg)	129	0.204	79.2 +0.17*AGE	0.020
End-tidal CO_2 (%)	119	0.264	42.2 +0.070*AGE	0.004
Heart rate (beats/min)	126	0.212	71.3 +0.12*AGE	0.017
CrCP (mm Hg)	121	0.206	17.6 +0.20*AGE	0.024
Coherence LF	129	0.272	0.81 -0.0031*AGE	0.002
Gain LF	129	0.265	1.45 -0.0081*AGE	0.002

n, number of participants (see Methods for exclusion criteria); CC, correlation coefficient; CBFV, cerebral blood flow velocity; MBP, mean arterial blood pressure; CrCP, critical closing pressure; RAP, resistance-area product; ARI, cerebral autoregulation index; VLF, very low frequency; LF, low frequency.

FIGURES

Figure 1

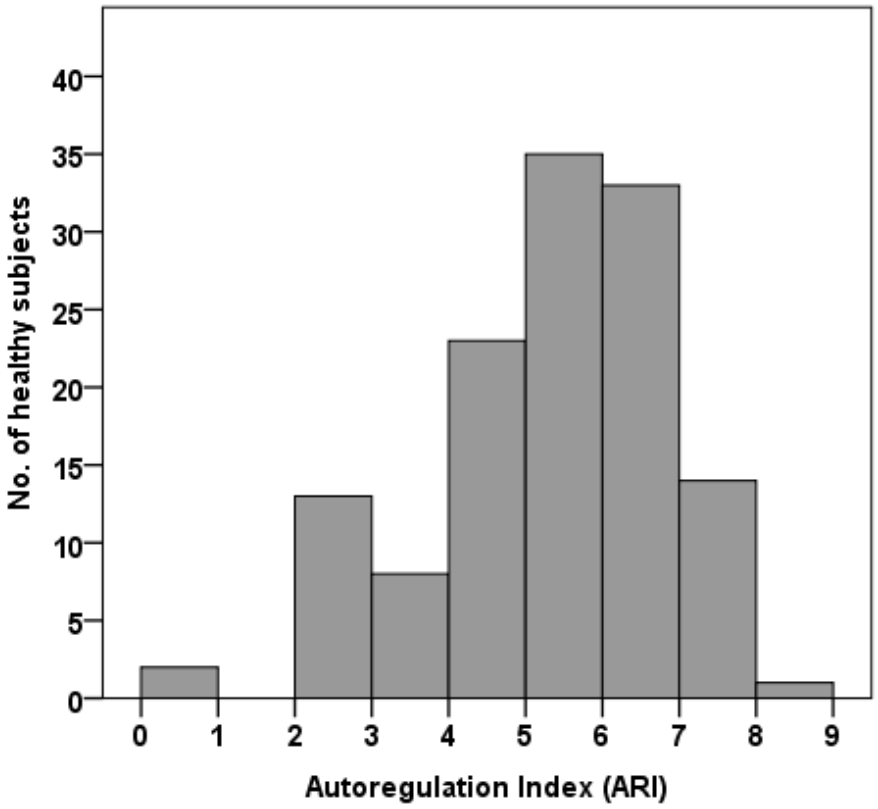

Figure 2