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Impact of hypertension on cerebral microvascular structure in CPAP-treated obstructive sleep apnoea patients: a diffusion magnetic resonance imaging study

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Abstract

Purpose Obstructive sleep apnoea (OSA) is a highly prevalent sleep-related breathing disorder associated with hypertension, impaired peripheral vascular function and an increased risk of stroke. Evidence suggests that abnormalities of the cerebral microcirculation, such as capillary rarefication, may be present in these patients. We evaluated whether the presence of hypertension may affect the cerebral capillary architecture and function assessed by Intravoxel Incoherent Motion (IVIM) magnetic resonance imaging (MRI) in patients with continuous positive airway pressure (CPAP)-treated OSA.

Methods Forty-one patients (88% male, mean age 57 ± 10 years) with moderate-to-severe OSA were selected and divided into two groups (normotensive vs. hypertensive). All hypertensive OSA patients were adherent with their antihypertensive medication. Cerebral microvascular structure was assessed in grey (GM) and white matter (WM) using an echo-planar diffusion imaging sequence with 14 different *b* values. A step-wise IVIM analysis algorithm was applied to compute true diffusion (*D*), perfusion fraction (*f*) and pseudo-diffusion (*D**) values. Group comparisons were performed with the Wilcoxon-Mann-Whitney-Test. Regression analysis was adjusted for age.

Results Diffusion- and perfusion-related indexes in middle-aged OSA normotensive patients were quantified in both tissue types (*D* [10^{-3} mm^2/s]: GM = 0.83 ± 0.03; WM = 0.72 ± 0.03; *f* (%) GM = 0.09 ± 0.01; WM = 0.06 ± 0.01; *D** [10^{-3} mm^2/s]: GM = 7.72 ± 0.89; WM = 7.38 ± 0.98). In the examined tissue types, hypertension did not result in changes on the estimated MRI IVIM index values.

Conclusion Based on IVIM analysis, cerebral microvascular structure and function showed no difference between hypertensive and normotensive patients with moderate-to-severe OSA treated with CPAP. Treatment adherence with antihypertensive drug regime and, in turn, controlled hypertension seems not to affect microvascular structure and perfusion of the brain.

Trial registration ClinicalTrials.gov Identifier: NCT02493673

Keywords Obstructive sleep apnoea · Cerebral microvascular structure · Magnetic resonance imaging · Hypertension

ST and TG contributed equally to this work.

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Abbreviations

AHI	apnoea-hypopnoea-index
BP	blood pressure
CPAP	continuous positive airway pressure
ESS	Epworth Sleepiness Scale
HR	heart rate
ODI	oxygen desaturation index
OSA	obstructive sleep apnoea

Introduction

Sleep-disordered breathing characterized by repetitive apnoeas and hypopneas causes intermittent hypoxia and hypercapnia, an

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elevated sympathetic drive, and leads to surges in blood pressure [1]. Obstructive sleep apnoea (OSA), characterized by a collapse of the upper airway, affects around 34% of males aged 30–70 years and 17% of women aged 30–70 years [2, 3]. An association between OSA and several cardiovascular comorbidities, such as hypertension, increased risk of stroke and heart failure has been described previously [4–6]. Furthermore, sympathetic activation associated with OSA seems to contribute to a higher occurrence of therapy-resistant arterial hypertension and might blunt nocturnal blood pressure dipping [7].

Chronic arterial hypertension induces specific alterations of the microvascular vessel architecture, such as capillary rarefication [8–11]. A causal relationship of OSA on elevated blood pressure has been shown in meta-analyses and blood pressure improves under treatment with continuous positive airway pressure (CPAP), as well as with adherence to an antihypertensive drug regimen [12, 13]. However, uncontrolled blood pressure fluctuations, correlating with increases of intracranial pressure during apnoeic episodes, could potentially lead to capillary damage and changes in the vessel microarchitecture. These changes have already been described for the retina or the forearm [14, 15]. Skin capillary density of the forearm and the periungual field, as an expression of structural vessel rarefication—measured with videocapillaroscopy—was also reported to be reduced in OSA patients [16]. Some authors suggested that capillary rarefication could be partially reversible through regular use of antihypertensive medication [15]. Whether these changes also apply for cerebral capillary architecture in patients with OSA is currently unclear.

Intravoxel incoherent motion (IVIM) is a magnetic resonance imaging (MRI) technique proposed by Le Bihan et al. in 1986 [17]. This method enables the quantification of random water molecules dynamics within the image voxel. In biological tissues, both molecular diffusion and microcirculation of blood in the capillary network can be detected using IVIM [18]. As shown by Le Bihan and Turner, the derived parameters can be related to traditional perfusion indexes such as cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time for a given capillary geometry [19]. Perfusion-related effects can be detected by applying weak diffusion-encoding gradients (so-called low b values), while further signal attenuation at high b values is expected to be mainly dominated by the thermal-driven diffusion. The perfusion-related parameters (D^* and f) and the diffusivity parameter D allow monitoring of the integrity and density of the capillary network of different tissues [20–22]. In brain tumours, it was proposed to use the f value to directly assess the vascular volume fraction, as this parameter reflects the fraction of incoherent signal arising from the microvascular component within the voxel. A significant correlation between the f values and the histological confirmed vascular density was described, pointing out the advantage of a non-invasive and quantitative measurement method to directly assess the volume fraction of capillaries in a specific brain volume [23].

So far, no IVIM-MRI data have been reported for the assessment of cerebral capillary structure in OSA patients. The aim of this study was to provide benchmark values of cerebral IVIM parameters for middle-aged normotensive OSA patients. Additionally, IVIM was performed in treatment-adherent hypertensive age-matched subjects with OSA to evaluate if therapeutically controlled hypertension affects cerebral capillary structure and function as estimated by IVIM-MRI.

Methods

Subjects

Forty-one patients with moderate-to-severe OSA were included in this prospective study. Inclusion and exclusion criteria of the study participants are listed in Table 1. Patients were allocated to the two groups according to the diagnosis of arterial hypertension and antihypertensive drug treatment [24]. The patients in this study were treated with CPAP for at least 1 year before inclusion. All patients were highly compliant regarding their CPAP treatment according to the data downloaded from the personal CPAP machine. In hypertensive subjects, blood pressure was well controlled due to the use of antihypertensive drugs and treatment compliance.

This post hoc analysis is part of randomized controlled trial, which was approved by the Cantonal Ethics Committee of Zurich (KEK-ZH-No. 2014-0684, ClinicalTrials.gov Identifier: NCT02493673), and all procedures in this trial involving human participants were performed in accordance with the ethical standards of the local ethical committee as well as the 1964 Helsinki declaration and its later amendments [25]. We obtained written informed consent from all participants.

Baseline blood pressure and heart rate

Blood pressure (BP) and heart rate (HR) were measured in triplicate in the morning of the MRI appointment; the average of three measurements was used for further analysis.

MRI protocol

The MRI data were acquired using a 3-T whole-body scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). Signals were recorded using a 64-channel head coil, while the built-in body transmit coil was used for spin excitation. A three-dimensional T1-weighted Magnetisation-Prepared Rapid Gradient-Echo (MPRAGE) sequence (TR = 7 ms, TE = 2.32 ms, flip angle = 8°, TI = 900 ms, parallel

Table 1 Inclusion and exclusion criteria for the participants

Inclusion criteria	Exclusion criteria
1. Age 20–75 years	1. Previous cerebral stroke
2. Apnoea-hypopnoea-index (AHI) and/or oxygen desaturation index (ODI4%) ≥ 20/h in their in-laboratory sleep study at the time of diagnosis	2. Known cerebral vascular anomalies
3. Treated with CPAP for at least 1 year with high compliance (device usage ≥ 4 h/night on at least 80% of the past 365 days with a current AHI ≤ 10/h, measured from the CPAP machine download data)	3. Carotid artery stenosis ≥ 70%
4. ODI4% ≥ 15/h in a current nocturnal pulse oximetry during a 5 night period off CPAP treatment	4. Use of alpha-and beta-adrenergic blocking medication
5. Informed consent	6. Antianginal medications, triptans or selective cyclooxygenase (COX)-inhibitors
	7. Unstable, or untreated, coronary or peripheral artery disease
	8. Inadequately controlled arterial hyper- or hypotension (≥ 180/110 or ≤ 90/60 mmHg)
	9. MRI-incompatible implants, pacemakers and internal cardiac defibrillators, coronary artery stents
	10. Previous ventilatory failure (awake SpO2 ≤ 93% and/or PaCO2 ≥ 6 kPa)
	11. Cheyne-Stokes breathing
	12. Professional driving
	13. Previously reported sleep-related traffic accidents
	14. Chronic obstructive pulmonary disease

imaging using GRAPPA, acceleration factor 2) was acquired for anatomical orientation. The sequence protocol included an echo-planar imaging (EPI) sequence for the acquisition of diffusion-weighted images (DWI) of the neurocranium. Diffusion-encoding was performed using the following *b* values: 0, 5, 10, 20, 35, 55, 80, 110, 150, 200, 300, 500, 750, 1000 s/mm^2 and applying the diffusion-encoding gradients along three orthogonal directions. Additional sequence parameters were TR = 6400 ms, TE = 90 ms, readout bandwidth = 1685 Hz, voxel size = 2.0 × 2.0 × 2.0 mm^3.

MRI data processing

Before processing of the MR signal, diffusion-weighted images were realigned to the first b0 volume using the "diffusion" toolbox of Statistical Parametrical Mapping (SPM) 12, (Wellcome Trust Centre for Neuroimaging, London, UK).

For each subject, grey matter (GM) and white matter (WM) tissue probability volumes were generated using the segmentation tool of SPM on the basis of the T1-weighted anatomical reference. Tissue probability values lower than 0.95 were set to zero to generate WM and GM masks. The derived tissue masks were coregistered to the b0 volume of the diffusion-weighted volume using SPM.

The diffusion-weighted signal can be modelled using a bi-exponential function depending on: the pseudo-diffusion coefficient, *D**, which describes microscopic incoherent movement attributed to the effect of the blood flowing in the randomly distributed microvascular capillary segments; the diffusion coefficient, *D*, and the perfusion fraction, *f*, i.e. the percent of voxel volume occupied by capillaries [14]. Multiple *b* value signal was fitted to the following equation, according to the IVIM model proposed by Le Bihan et al. [17]:

$$\frac{Sb}{S0} = f \cdot exp\left(-bD^{*}\right) + (1-f) \times exp(-bD) \quad (1)$$

In the previous equation, Sb and S0 represent the signal intensities acquired at the *b* value *b* and 0 s/mm^2, respectively. *D** is the pseudo-diffusion coefficient related to capillary perfusion, *f* is the perfusion fraction indicating the voxel volume occupied by perfused capillaries (value ranging between 0 and 1), and *D* represents the pure diffusion coefficient of passive molecular water diffusion.

A step-wise approach was applied for the derivation of the IVIM parameters starting from Eq. 1 [26]. For *b* values higher than 200 s/mm^2, the signal attenuation was assumed to be dominated by the molecular diffusion. In this case, the diffusion coefficient, *D*, and the intercept

of the high b value fit to the b = 0 s/mm^2, S_{int}, were estimated by linear fitting of the logarithm of the signal, S_b, to the function:

$$\ln(S_b) = \ln(S_{int}) - b \cdot D \quad (2)$$

The fraction of perfusion, f, was then approximated as

$$f = \frac{S_0 - S_{int}}{S_0} \quad (3)$$

The pseudo-diffusion coefficient, D*, was subsequently estimated by bi-exponential fitting of the signal to Eq. 1 while keeping D and f constrained. IVIM parameters were computed from the signal averaged over the whole segmented grey matter and white matter, respectively.

Statistical methods/data analysis

Normally distributed data are expressed as mean (SD) unless stated otherwise. Comparison between characteristics of the group was performed using the Wilcoxon-Mann-Whitney U test (continuous variables) and a linear regression where we adjusted for the additional variable age. A two-sided significance level of < 0.05 was used to determine statistical significance. The statistical analysis was performed in R (R Core Team, Vienna Austria 2013, R version 3.4.4 [2018.03.15]).

Results

Baseline patient characteristics

Overall 41 patients participated in this study. The normotensive OSA group comprised 21 subjects. In the hypertensive OSA group, 20 patients were included. With the exception of the hypertensive condition, the two groups were similar in all relevant characteristics listed in Table 2.

IVIM measurements

IVIM measurements were conducted in all 41 patients. Image quality allowed the computation of the IVIM indexes in all subjects and in both tissue types (Figs. 1 and 2). For the GM, a mean diffusion coefficient D of 0.83 ± 0.03 10^{-3} mm^2/s was computed in the normotensive group, with no significant differences to the mean values derived in the hypertensive cohort (0.86 ± 0.10 10^{-3} mm^2/s, $p = 0.62$). Slightly lower diffusion coefficients as compared to the GM were measured over the WM in both sub-cohorts ($D_{\text{normotensive}} = 0.72 \pm 0.03$ 10^{-3} mm^2/s, $D_{\text{hypertensive}} = 0.77 \pm 0.11$ 10^{-3} mm^2/s; $p = 0.94$).

The perfusion-related indexes were higher in the GM than in the WM (Table 3), with no significant differences between the two sub-groups (Fig. 3). A fraction of perfusion (f) of 0.09 ± 0.01 was measured in the GM of the normotensive sub-group (hypertensive group: 0.10 ± 0.04, $p = 0.44$). The D* values were measured in both tissue types and in both sub-groups leading to the following values: $GM_{\text{normotensive}}$ =

Table 2 Baseline characteristics of the trial population

	Normotensive group $n = 21$	Hypertensive group $n = 20$	p value
Male, n (%)	19 (90.5)	17 (85.0)	$p = 0.59$
Age (years)	54.95 ± 10.62	58.95 ± 9.34	$p = 0.21$
Height (cm)	174.29 ± 10.56	174.95 ± 8.99	$p = 0.83$
Weight (kg)	103.14 ± 15.59	103.27 ± 21.18	$p = 0.98$
BMI (kg/m^2)	34.31 ± 6.92	33.63 ± 6.04	$p = 0.74$
Neck circumference (cm)	44.15 ± 3.06	44.60 ± 4.45	$p = 0.71$
Apnoea-hypopnoea-index (h^{-1})	4.56 ± 3.08	6.73 ± 5.65	$p = 0.13$
Oxygen desaturation index (h^{-1})	3.92 ± 3.93	5.37 ± 5.75	$p = 0.35$
Mean systolic blood pressure (mmHg)	112.36 ± 18.70	124.34 ± 22.13	p = 0.07
Mean diastolic blood pressure (mmHg)	79.75 ± 7.72	81.02 ± 9.68	$p = 0.64$
Mean heart rate (bpm)	65.01 ± 7.74	66.45 ± 8.17	$p = 0.57$
Epworth sleepiness scale (points)	6.81 ± 3.91	8.80 ± 4.19	p = 0.12
Diabetes, n (%)	19 (90.5)	12 (60.0)	$p = 0.02$
Coronary artery disease, n (%)	1 (4.8%)	4 (20.0%)	$p = 0.14$
Heart failure, n (%)	0 (0.0%)	1 (5.0%)	$p = 0.30$
Dyslipidaemia, n (%)	1 (4.8%)	3 (15.0%)	$p = 0.27$
Obesity, n (%)	16 (76.2%)	15 (75.0%)	$p = 0.93$

Data presented in mean ± standard deviation

BPM beats per minute

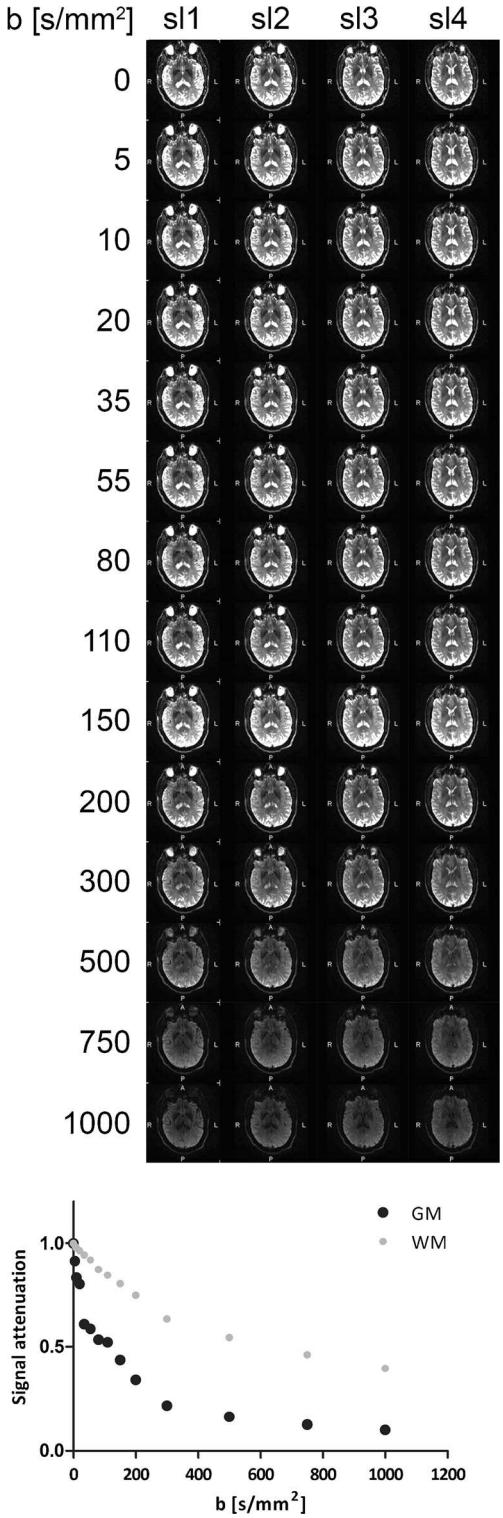

Fig. 1 Diffusion-weighted images acquired over three slices in one participant show good image quality for signal modelling. In the diagram, the signal attenuation measured over the white and the grey matter shows the typical bi-exponential pattern of IVIM

$7.7 \pm 0.9\ 10^{-3}$ mm^2/s ($GM_{hypertensive} = 8.5 \pm 2.1\ 10^{-3}$ mm^2/s, $p = 0.07$) and $WM_{normotensive} = 7.38 \pm 0.98\ 10^{-3}$ mm^2/s ($WM_{hypertensive} = 8.03 \pm 1.97\ 10^{-3}$ mm^2/s, $p = 0.12$).

Discussion

The aims of this study were (1) to provide benchmark cerebral IVIM values for middle-aged OSA patients and (2) to additionally investigate if potential differences in the capillary bed between normotensive and pharmacologically controlled hypertensive OSA patients are detectable using IVIM-MRI. The study relies on scientific findings suggesting a potential systemic involvement of the capillary network in OSA subjects [16]. In animal models of hypertension as well as in hypertensive humans, capillary rarefication has been documented for different microvascular beds, i.e. muscle, skin or brain tissue [23, 27, 28]. Furthermore, low capillary density has been found in women with pre-eclampsia, thus indicating that capillary rarefication might contribute to the failure of blood pressure auto-regulation in this condition [29]. In this context, the coexistence of both hypertension and OSA might suggest a further deterioration of capillary morphology and function and promote the progress of cardiovascular diseases. In our study, however, no significant differences were found in the IVIM parameters computed for the cerebral white and grey matter comparing normotensive OSA subjects with treatment-adherent hypertensive OSA subjects.

In the brain, a delicate equilibrium is necessary between substrate delivery and energy demands caused by neural activity. The relationship between neural activation and blood flow has not been fully elucidated, but because capillaries account for almost 50% of the cerebrovascular resistance, they play an important role [30, 31]. Therefore, although a systemic effect was suspected, local compensatory effects may be responsible for the conservation of parenchymal diffusivity, microvascular structure and microvascular perfusion within comparable values in both cohorts [31]. A further point is related to the possibility suggested in the literature that pharmacological antihypertensive therapy may reverse rarefication and potentially associated dysfunction in capillaries [15, 32]. Finally, moderate changes in blood flow associated with the hypertensive condition may be now detectable by using the IVIM metrics [33, 34].

While values for the pseudo-diffusion coefficient reported in this study are in accordance with reference values reported in young healthy volunteers, slight deviations were detected in the computed values for molecular diffusion (D) and in the fraction of perfusion [35]. Molecular diffusion values for both, white and grey matter, are slightly higher in the investigated group of patients compared to values measured in young healthy volunteers [35, 36]. The values in young healthy subjects for D is in the order of 0.71 ± 0.28 to 0.84 ± 0.05 10^{-3} mm^2/s for the GM and 0.66 ± 0.03 to 0.77 ± 0.04 10^{-3} mm^2/s for the WM [35, 36]. This result may partially be attributed to the dependency of the water diffusion coefficient on subject's biological age. Postmortem investigations of brain anatomical microstructure in normal ageing provided

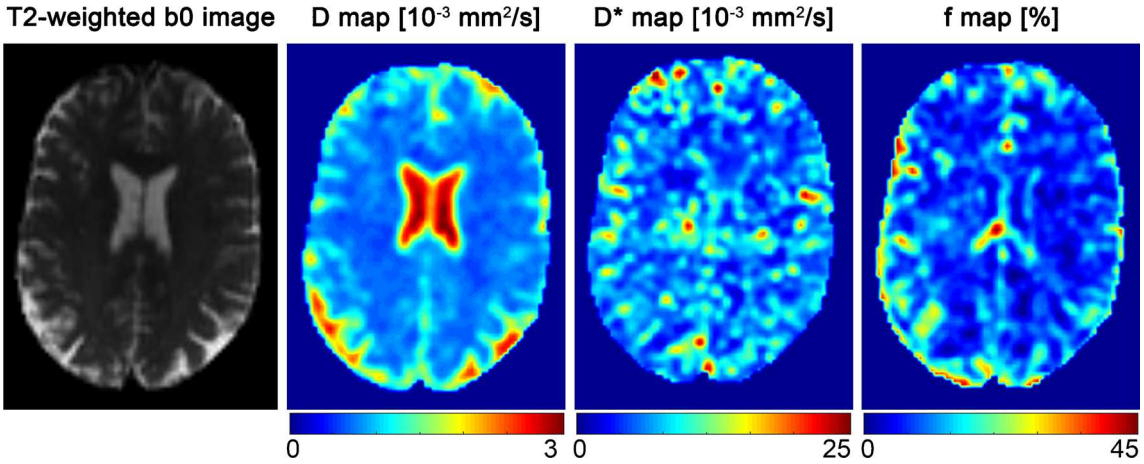

Fig. 2 Representative parametrical maps computed in one normotensive patient (male, 53 years old) are reported; the T2-weighted b0 image serves as anatomical reference. Differences in the IVIM parameters between GM and WM result in a clear contrast between tissue types, which is dominated by blood perfusion in the *D** and in the *f* map

evidence of an increase of the molecular diffusion within the white matter and has been attributed to breakdown of myelin sheathing, disruption of the microtubules and enlargement of the interstitial space [37]. In line with these findings, Pfefferbaum et al. demonstrated that deep grey matter brain structures also exhibit an increase in molecular diffusion, assessed by diffusion tensor imaging, in elderly subjects [38]. Furthermore, higher *D* values were described in patients with cerebral small vessel disease reflecting microstructural tissue impairment in this condition [39].

In our study, OSA patients showed a slightly lower fraction of perfusion than reported in the literature for young healthy patients [35, 36]. Although no studies have so far investigated the longitudinal effect of normal ageing on the cerebral perfusion IVIM parameters, a dependency of cerebral blood flow on biological age has been reported using techniques of arterial spin labelling (ASL) MRI [40]. Interestingly, Wong et al. reported an unexpected increase in the fraction of perfusion in patients with cerebral small vessel disease (cSVD) [39]. This finding was interpreted as a potential effect of vasodilation, and, in turn, more flowing water molecules, enlarged perivascular spaces and vessel tortuosity leading to the assumption that perfusion volume fraction might not be purely blood flow related in cSVD [39]. Several other mechanisms were suggested to contribute to the CBF decreases in ageing, such as microvascular deterioration, reduced vascular density and impaired angiogenesis [41]. In a recent publication, absolute and relative perfusion decreases, assessed via ALS fMRI, were found in an elderly group of cognitive healthy patients, regarding frontal, parietal and occipital regions when compared to young subjects [42]. These results were in line with subsequent studies reporting hypoperfusion in several areas [43]. Furthermore, age-related reductions in CBF could be partly explained due to grey matter atrophy or loss. As cortical thinning occurs with age, this results in increased partial volume effects [44]. These partial volume effects were described to account for up to 12% of the age-related CBF differences [43]. As the typical OSA patient is around 60 years and predominantly male, our benchmark values can only partially be compared to the above-mentioned pre-existing studies including younger

Table 3 Primary outcomes by group

		Normotensive group $n = 21$	Hypertensive group $n = 20$	p value*	Adjusted p value**
Grey matter	D [10^{-3} mm^2/s]	0.83 ± 0.03	0.86 ± 0.10	$p = 0.62$	$p = 0.65$
	f	0.09 ± 0.01	0.10 ± 0.04	$p = 0.42$	$p = 0.64$
	D^* [10^{-3} mm^2/s]	7.72 ± 0.89	8.54 ± 2.10	$p = 0.07$	$p = 0.87$
White matter	D [10^{-3} mm^2/s]	0.72 ± 0.03	0.77 ± 0.11	$p = 0.94$	$p = 0.07$
	f	0.06 ± 0.01	0.08 ± 0.05	$p = 0.17$	$p = 0.54$
	D^* [10^{-3} mm^2/s]	7.38 ± 0.98	8.03 ± 1.97	$p = 0.20$	$p = 0.48$

*Wilcoxon-Mann-Whitney-Test

**Regression analysis adjusted for age

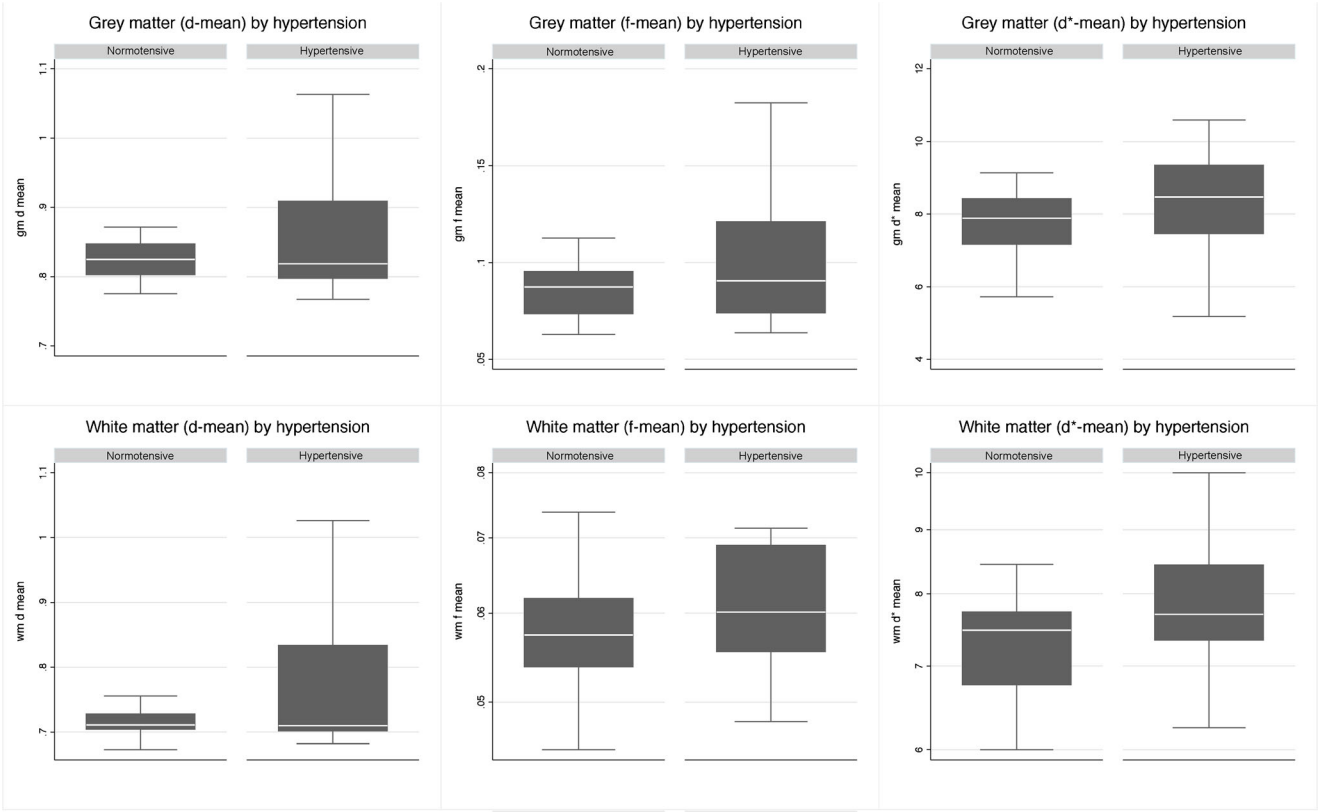

Fig. 3 Boxplots graphically represent the distribution of the IVIM parameters for both cohorts (normotensive versus hypertensive) and in each tissue type (grey matter, white matter). None of the differences were statistically significant ($p > 0.05$)

controls. As we did not perform the analysis of special regions of interest, we may have missed these subtle effects.

Besides the potential effect of ageing, the lower fraction of perfusion in OSA patients may be attributable to a pathological degeneration of the microcirculatory bed, by now not studied or described. It is still discussed if capillary rarefication is a cause or consequence of hypertension [11]. But as this phenomenon is described even in early hypertension, this could be suggestive for changes in the microarchitecture preceding initiation of antihypertensive treatment.

This study has several strengths, one major advantage being the carefully selected group of patients without any known major vascular anomalies or stroke. Furthermore, all MRI data were analysed and checked for structural defects by a specialist in neuroimaging. The whole cohort had a high adherence with both CPAP treatment and treatment with their antihypertensive drug regime. Patients using medication potentially affecting cerebral perfusion were excluded. All scans were performed during 07.00 and 09.00 a.m. in the morning to exclude any major confounding factors contributed to the time of scanning, as this may have influenced the results. A standardized measurement protocol was applied that included a predefined time in supine position of minimum 15 min before scanning for all patients to reduce intersubject variability.

Moreover, it is important to mention potential study limitations. Because this is a post hoc analysis, sample size might be limited [25]. This limited the measurement time which could be dedicated to the IVIM evaluations. Second, in compliance with the ethical agreement of the trial, we did not include a healthy control group in this investigation and are unable to compare results with an age- and sex-matched group. Indeed, capillary rarefication in hypertensive patients with and without sleep apnoea has already been described in the literature before [16]. Nazzaro et al. investigated skin capillary density in hypertensive patients with and without sleep apnoea [16]. Furthermore, they divided their patient groups according to the severity of OSA. Their main finding was that in untreated mild hypertensive patients, it was the severity rather that the presence of OSA that was accompanied by exacerbated capillary rarefication [16]. As with a systematic disease like hypertension, it is suggestive that different organs are affected by the consequences. Ultimately, controlled trials with a higher sample size and parallel assessment of microvascular structures at different organ sites are warranted. Finally, the generalizability of the conclusions might be limited due to the overrepresentation of men in the study sample.

In conclusion, this study provides for the first time cerebral IVIM benchmark values for normotensive OSA subjects. Overall, IVIM indexes, as a measure of cerebral microvascular structure and function, assessed via IVIM-MRI showed no difference between treatment-adherent hypertensive and normotensive OSA patients. Treatment adherence with antihypertensive drug regime and, in turn, controlled hypertension is not a condition affecting microvascular structure and perfusion as estimated by IVIM-MRI.

Author contributions Conception and design: MK, CR, AB. Funding: MK. Trial conduct: ST, FL. Analysis and interpretation of data: ST, FL, TG, CR, MK, AB, SW. Drafting the article: ST. Revising the article for important intellectual content and final approval: all authors.

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Compliance with ethical standards

Conflict of interest The authors declare the following conflicts of interest: ST, FL, CR, SW and AB have nothing to disclose. MK reports grants from University of Zurich and grants from Lunge Zurich during the conduct of the study. MK and TG report personal fees from Bayer AG, outside the submitted work.

Ethical approval All procedures performed in the 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.

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

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