



Early microvascular cerebral blood flow response to head-of-bed elevation is related to outcome in acute ischemic stroke

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Received: 29 November 2018 / Revised: 31 January 2019 / Accepted: 1 February 2019 / Published online: 9 February 2019
  Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Background and aims Previously, microvascular cerebral blood flow (CBF) response to a mild head-of-bed (HOB) elevation has been shown to be altered in acute ischemic stroke (AIS) by diffuse correlation spectroscopy (DCS). We have hypothesized that early CBF response is related to the functional outcome.

Methods Patients with a non-lacunar AIS in the anterior circulation were monitored by DCS to measure relative CBF ($\Delta rCBF$) on the frontal lobes bilaterally during a 0 –30  HOB elevation at early (≤ 12) or late (> 12) hours from symptom onset. National Institutes of Health Stroke Scale (NIHSS) scores were recorded at baseline at 24 and at 48 h. Functional outcome was measured by the modified Rankin Scale (mRS) at 3 months.

Results Thirty-eight ($n = 38$) AIS patients [baseline NIHSS = 19 (interquartile range: 16, 21)] were studied. $\Delta rCBF$ decreased similarly in both hemispheres ($p = 0.4$) when HOB was elevated and was not associated with baseline and follow-up NIHSS scores or patient demographics. At the early phase ($n = 17$), a lower or paradoxical $\Delta rCBF$ response to HOB elevation was associated with an unfavorable functional outcome (mRS > 2) in the ipsilesional (but not in the contralesional) hemisphere ($p = 0.010$). $\Delta rCBF$ response in the late acute phase was not related to mRS.

Conclusions Early CBF response to mild HOB elevation in the ipsilesional hemisphere is related to functional outcome. Further studies may enable optical monitoring at the bedside to individualize management strategies in the early phase of AIS.

Keywords Ischemic stroke · Outcome · Cerebral blood flow · Brain perfusion · Diffuse correlation spectroscopy · Near-infrared spectroscopy

Introduction

Although recent advances in reperfusion therapy and organized stroke care in specialized stroke units have led to better outcomes in stroke patients, current therapies have limited availability and efficacy [1]. Therefore, it is

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00415-019-09226-y>) contains supplementary material, which is available to authorized users.

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still crucial to improve management strategies to benefit more stroke patients.

Flat head-of-bed (HOB) positioning is a management strategy that has been often used as a widely available method to promote increased cerebral perfusion in the clinics [2]. The specifics of cerebral blood flow (CBF) changes due to HOB positioning after AIS-related brain injury have been studied in transcranial Doppler (TCD) and optical studies [3–8]. A systematic review and meta-analysis of TCD studies found that mean cerebral blood flow velocities (CBFV) increased in the side of the affected major cerebral arteries when the patients were positioned in the lying-flat HOB position [9]. However, the clinical benefits are uncertain and contradictory [10, 11] which could be due to individual variability.

Recent research with diffuse correlation spectroscopy (DCS) [12, 13] that uses the temporal fluctuations of near-infrared light to measure cortical microvascular CBF non-invasively has provided evidence that the cerebral hemodynamic response to HOB positioning is heterogeneous among individuals after brain injury [3, 4, 14] and is otherwise relatively homogeneous [15]. In patients with AIS, an inter-hemispheric asymmetry was observed including a paradoxical response identified in $\approx 25\%$ of the cases [3, 4], which was not detected in simultaneous TCD monitoring, suggesting that DCS may be superior for monitoring collateral blood flow dynamics during posture changes [4]. Similarly, hemodynamic response to HOB position alterations was shown to be a biomarker of clinical status in obstructive sleep apnea patients [16].

We have, therefore, hypothesized and tested that this method may detect abnormalities in the cerebrovascular reactivity and its changes in response to a therapy. In particular, this method may be a biomarker of the functional outcome after AIS as the role of collateral flow is linked to the recovery of penumbra. If so, this protocol can be used for individualization of therapies including the selection of earlier optimal positioning to improve the benefits of postural and mobilization therapies on functional outcome.

Aims

In this study, we investigated the relationship between the cortical CBF response to HOB changes measured by DCS at different times after the symptom onset and the functional outcome of patients with AIS. We have hypothesized that the cortical CBF response to HOB changes during the earlier phases of AIS is a biomarker of CBF autoregulation and, therefore, is associated with functional outcome after stroke.

Methods

This study was conducted at the Stroke Unit of Hospital de la Santa Creu i Sant Pau (Barcelona, Spain) from 2015 to 2017, whose protocol was approved by the Ethical Committee (EC/15/130). The participants or their legal proxies gave written consent to participate.

Patients with an acute non-lacunar AIS in the anterior circulation of less than 48 h from the symptom onset were recruited for bilateral monitoring of CBF in the frontal lobes during a HOB elevation from supine (0°) to 30° . The inclusion criteria were being older than 18 years, National Institutes of Health Stroke Scale (NIHSS) of more than three at admission and pre-stroke modified Rankin scale (mRS) of less than three. The exclusion criteria were resting heart rate less than 40 or greater than 110 beats per minute, peripheral arterial oxygen saturation less than 92% with supplementation, diagnosis of transient ischemic attack, minor stroke, or posterior circulation AIS.

Head-of-bed (HOB) manipulation protocol

All patients were placed flat (HOB 0° – 15°) during the first 24 h except when being measured according to the local practice. Afterwards, mobilization was initiated according to the judgment of the clinician.

During the study (Fig. 1), first, the patient was placed in supine position (0°) for at least 30 min. Afterwards, data were acquired for 5 min each at baseline supine and at 30° elevation. Finally, the patient was returned back to the flat position (0° – 15°). The transition between the HOB positions was recorded and lasted a maximum of 30 s. The protocol was repeated up to four times at intervals of 48 h during the first week of admission if the patient was stable.

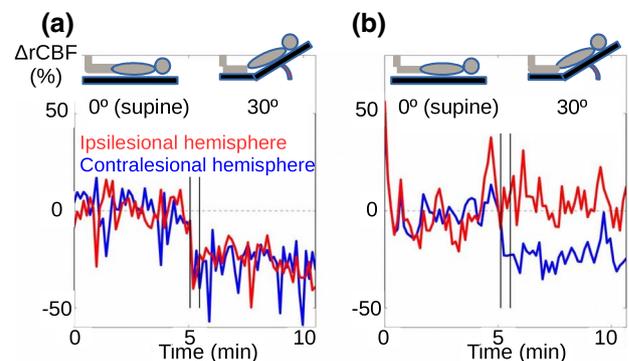


Fig. 1 Continuous optical measurement showing **a** an expected $\Delta rCBF$ response and **b** a paradoxical response in one hemisphere (ipsilesional hemisphere) for two patients. Vertical lines indicate the period when body position was changed

Optical methods and instrumentation

The custom built diffuse correlation spectroscopy [13] system and the analysis methods were previously described [17] and validated [13]. Cerebral blood flow was monitored continuously every 2.5 s and $\Delta rCBF$ changes were obtained by dividing the continuous blood flow index by this mean baseline CBF. The change in CBF between 0° and 30° ($\Delta rCBF_{30}$) is reported as the average of the first to 4 min at 30°.

A paradoxical response was defined as an increase of $\Delta rCBF_{30} > 2\%$ or “no change”, which was defined as the coefficient of variation measured in healthy subjects [18].

Clinical and imaging evaluation

Baseline examinations included the collection of demographics and vascular risk factors and a physical examination. The stroke severity was assessed with the NIHSS at admission, at the moment of the measurement, at 24 and at 48 h from stroke onset, and at discharge. Early clinical deterioration was defined as an increase of at least four points of the 48 h NIHSS score compared to the baseline. The etiologic stroke subtype was classified according to the modified Trial of Org 10 172 in Acute Stroke Treatment (TOAST) criteria.

At admission, a cranial computed tomography (CT) and vascular imaging with either CT angiography or color-coded duplex sonography were performed. The extent of early ischemic changes was evaluated by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS). The presence of frontal cortical signs of ischemia in the ipsilesional hemisphere (M1 of the ASPECTS score) was also evaluated separately.

If relevant, recanalization was assessed by transcranial duplex before our protocol. Functional outcome was evaluated at 3 months by the mRS. A score of > 2 was considered indicative of an unfavorable functional outcome. All the neurological scales were obtained by experienced clinicians blinded to the optical information.

Statistical analysis

We have expressed quantitative variables as a median and an interquartile range [median (Q1, Q3)], and categorical variables as number of cases and percentages. Wilcoxon rank-sum test was used to assess the difference of the change in cerebral blood flow between 0° and 30° ($\Delta rCBF$ supine to 30°) responses between with and without good functional outcome (favorable, $mRS \leq 2$) when only the first measurement for each patient was used. The Wilcoxon rank-sum test (for quantitative variables) or the Chi-squared test (for categorical variables) was used to assess differences on the clinical and demographic variables between paradoxical

and non-paradoxical responses, using Bonferroni correction when categorical variables presented more than two factors. The Wilcoxon signed-rank test was used to assess the $\Delta rCBF$ supine to 30° response between ipsi- and contra-lesional hemispheres and to assess if the $\Delta rCBF$ supine to 30° response was different from zero. We conducted a univariate linear mixed-effect model to assess clinical and radiological variables associated with $\Delta rCBF$ supine to 30°. Also, we conducted a univariate logistic mixed-effect model to assess clinical, radiological and optical variables associated with the dichotomized mRS ($mRS \leq 2$ vs $mRS > 2$) at 3 months. Patient identification number was considered to be a random factor for the mixed-effect models. Model fit was assessed using Chi-square tests on the log-likelihood values to compare the different models. Residuals plots were tested for the inspection of deviations from normality and homoscedasticity. All analyses were carried out in the R programming language and environment [19] and “nlme” software package was used. A p value < 0.05 was considered to be statistically significant.

Results

Clinical and radiological findings

We have studied 38 ($n = 38$) patients with an AIS in the anterior circulation. Table 1 contains the population demographics and clinical characteristics. The median age was 83 (68.75, 88) years. Median NIHSS score at admission was 19 (16, 21). At 3 months, the median mRS score was 4 (3, 6) and thirty-one patients ($n = 31$, 82%) were disabled ($mRS > 2$) or had died.

Head-of-bed position challenge findings

Median time from the stroke onset to the first optical measurement was 17 (7, 23) h. In one patient, the three repeated measurements performed in one hemisphere were excluded due to a frontal subcutaneous haematoma under the optical probe. Two additional measurements in one hemisphere each were excluded due to technical reasons. All patients tolerated HOB elevation and there were no study related side effects. Finally, a total of 72 ($n = 72$) measurements were analyzed.

Figure 1 shows representative typical and paradoxical responses of $\Delta rCBF_{30}$. Median $\Delta rCBF_{30}$ responses classified according to the different times from stroke onset, outcome and the presence of a paradoxical response are summarized in the Online Resource.

Overall, Table 2, median frontal $\Delta rCBF_{30}$ decreased significantly in both the ipsilesional [$- 3.1$ (-10.7 , 3.0)%, $p = 0.030$] and the contralesional hemispheres [$- 9.5$ ($- 15.8$, $- 3.5$)%, $p = 0.029$] in the first measurement. There

Table 1 Demographic and clinical variables of the study population ($n=38$)

Age (years)	83 (68.75, 88)
Male sex, n (%)	17 (44.7)
Arterial hypertension, n (%)	33 (86.8)
Dyslipidemia, n (%)	19 (50)
Diabetes mellitus, n (%)	8 (26.7)
Atrial fibrillation, n (%)	19 (50)
Time from symptoms onset to measurement (h)	17.1 (6.7, 23.1)
Ipsilesional extracranial ICA stenosis > 50%, n (%)	9 (23.7)
Thrombolysis, n (%)	25 (65.8)
Thrombectomy, n (%)	3 (7.9)
Intracranial occlusion (supraclinoid ICA or MCA), n (%)	29 (76)
Recanalization, n (%)	13 (34)
Occlusion in follow-up duplex, n (%)	12 (32)
Recanalization unknown, n (%)	13 (34)
Admission ASPECTS	9 (6.25, 10)
Ipsilateral cortical frontal ischemia, n (%)	7 (28)
TOAST	
Large artery atherosclerosis, n (%)	5 (13)
Cardioembolism, n (%)	13 (34)
Other etiology, n (%)	2 (5)
Undetermined etiology, n (%)	18 (47)
NIHSS at patient admission	19 (16, 21)
NIHSS at measurement	18 (7, 20)
Early neurological deterioration, n (%)	6 (16)
mRS at three months	4 (3, 6)
Disabled at three months (mRS > 2), n (%)	31 (82)
Death, n (%)	9 (24)

ICA Internal carotid artery, MCA middle cerebral artery

were no significant differences in ΔrCBF_{30} after HOB elevation between the ipsilesional and contralesional hemispheres ($p=0.387$).

When the measurements were grouped by time of the measurement, ΔrCBF_{30} was comparable between the early (≤ 12 h) and the late (> 12 h) phase for both the ipsilesional

and contralesional hemispheres ($p=0.357$ and $p=0.510$, respectively). In patients with serial measurements, there was no statistically significant difference between the first and the second measurements in the ipsilesional ($p=0.190$) or contralesional hemisphere ($p=0.890$).

In the first measurement performed, a unilateral or bilateral paradoxical response was present in 21 ($n=21$, 55%) patients (71% ipsilesional, 19% bilateral), which is further discussed in the Online Resource on the “The ΔrCBF_{30} paradoxical response” section.

When considering the presence of frontal cortical signs of ischemia in the ipsilesional hemisphere (M1 of the ASPECTS score), no interaction was found between the frontal hypodensity and the optical measurements ($p=0.416$). All patients with ischemic hypodensity ($n=7$, 28%) presented an unfavorable functional outcome. There were no clinical or radiological associated factors of the ΔrCBF_{30} response to HOB elevation in the early or late phase measurements or globally. For instance, the ΔrCBF_{30} response was not statistically significantly associated with either the early clinical course [deteriorated ($p=0.603$) or non-deteriorated ($p=0.587$)] or functional outcome at 3 months ($p=0.578$). An exception was the association with the mRS in the early phase, which is discussed below. Table 3 shows associations of clinical variables with the ΔrCBF_{30} in the early phase of stroke. No multivariate analysis was further performed since the statistical power of the study is not deemed to be sufficient to get into quantitative second order statistics.

Relationship between ΔrCBF_{30} and functional outcome

Figure 2 shows ipsilesional ΔrCBF_{30} versus the modified Rankin scale ($n=38$). When patients were divided according to the timing of the measurement, a statistically significant association between the ipsilesional ΔrCBF_{30} within the first 12 h (early phase) from stroke onset and the dichotomized mRS score at 3 months ($p=0.010$) was

Table 2 Median and interquartile ranges of ΔrCBF_{30} are shown grouped according to the time period of the first measurement and to the 3 months-mRS dichotomized score

	mRS ≤ 2 $n=7$	mRS > 2 $n=31$	p
ΔrCBF_{30} (%), ≤ 48 h ($n=38$)			
Ipsilesional	− 8.8 (− 13.5, − 5.5)*	− 2.5 (− 8.5, 4.9)	0.1
Contralesional	− 13.4 (− 15.9, − 10.5)*	− 5.1 (− 15.7, 4.9)	0.221
Paradoxical response	2.3, $n=2$	7.1 (3.0, 12.3)*, $n=25$	–
ΔrCBF_{30} (%), ≤ 12 h ($n=17$)			
Ipsilesional	− 10.4 (− 12.7, − 7.3), $n=4$	− 0.9 (− 4.4, 5.0), $n=13$	0.032
Contralesional	− 13.9 (− 15.6, − 7.9), $n=4$	− 14.0 (− 17.2, 7.4), $n=14$	0.878
Paradoxical response	5.6, $n=1$	9.1 (4.2, 27.4)*, $n=12$	–

* Indicates a statistically significant difference from zero

Table 3 Associations of $\Delta rCBF_{30}$ in the early phase of stroke with clinical variables

Univariate analysis	Beta	<i>p</i>
mRS dichotomized (mRS ≤ 2 vs mRS > 2)	1.57	0.010*
mRS numeric	2.79	0.015*
NIHSS	0.43	0.181
Age	0.14	0.571
Thrombolysis	-1.19	0.593
Thrombectomy	-5.80	0.595
Recanalization	-1.90	0.601

* Indicates a statistically significant model

observed (slope = 1.6, see Table 2; Fig. 2a). Fig. 2b shows that patients with a favorable functional outcome had a higher decrease of $\Delta rCBF_{30}$ in the ipsilesional hemisphere during the early phases (≤ 12 h), compared to those with an unfavorable functional outcome [-10.4 (-12.7, -7.3) and -0.9 (-4.4, 5.0) respectively, $p = 0.032$]. In contrast, the $\Delta rCBF_{30}$ response at later phases (> 12 h) was not related to functional outcome, $p = 0.878$, as shown in Fig. 2d, and no linear model could be fit (Fig. 2c).

Despite this association, $\Delta rCBF_{30}$ was not an associated factor of functional outcome at 3 months of follow-up. Remarkably, NIHSS was the only associated factor of functional outcome at 3 months ($p < 0.001$) with a slope of 1.24. Table 4 shows the results of the associations of clinical and optical variables with the dichotomized mRS at 3 months.

Fig. 2 Ipsilesional $\Delta rCBF_{30}$ versus mRS at early phase from stroke onset ($n = 17$) **a** as a continuous variable and **b** dichotomized according to functional outcome. Similarly, **c** and **d** correspond to the late phase ($n = 21$). The shaded region shows the 95% confidence intervals. (*) and (†) indicate a statistically significant linear model and difference between groups, respectively. Boxplots and labels show the median (interquartile range)

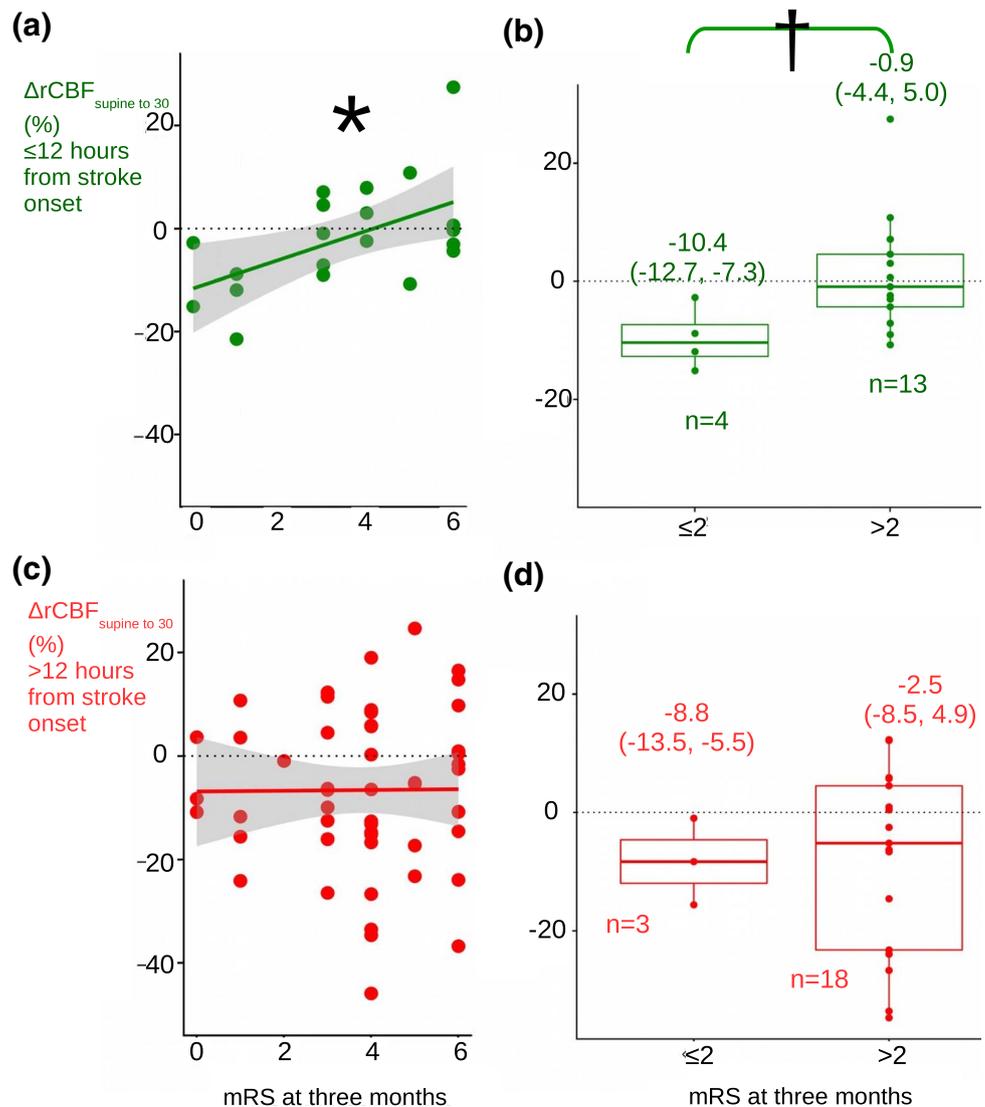


Table 4 Associations of the dichotomized mRS at 3 months with clinical and optical variables

Univariate analysis	Beta	<i>p</i>
$\Delta rCBF_{30}$ at early phase	0.62	0.669
NIHSS	1.24	<0.001*
Age	0.02	0.935
Thrombolysis	− 16.37	0.429
Thrombectomy	18.19	1.165
Recanalization	17.03	1.621

* Indicates a statistically significant model

Discussion

The main finding of our study is the association between the early phase, ipsilesional, microvascular CBF response to the changes of head positioning and the functional outcome in patients with anterior circulation AIS. The optical monitoring of CBF during HOB changes may, therefore, help to individualize future treatment strategies, including optimal positioning, after AIS.

Functional outcome at 3 months was related to the response of $\Delta rCBF_{30}$ to HOB changes occurring in the early phase (< 12 h after symptom onset), but not at later time points. This is relevant since the AIS morbidity is on the restoration of the CBF in the penumbra within a time window of cellular viability that depends on duration and severity of CBF cessation. Here, cerebral collateral circulation plays a major role in the recovery, and the timing when these collaterals are activated is important for their clinical effect. Early good collateral status is a strong predictor of better clinical outcome, while delayed collateral recruitment may indicate worse outcome [20]. Therefore, it could be expected that the response to collateral-enhancing stimuli, such as HOB positioning, may differ according to the timing from stroke onset.

Unlike this study, Favilla et al. failed to find an association between $\Delta rCBF_{30}$ within the first 72 h and stroke functional outcome [4]. This suggests that the impact of HOB positioning may be relevant during the early critical period, when potentially salvageable (penumbral) tissue is still present. Also, the higher stroke severity of our study sample may explain the difference between both studies.

Although $\Delta rCBF_{30}$ did not emerge to be the best predictor of functional outcome in the univariate logistic model in our study, its association deserves further research, as it represents a biomarker of a quantifiable effect that may enable the clinicians to personalize therapeutic strategies. The statistical power of the study, due to the size of the cohort recruited, may not be deemed to be sufficient to get into quantitative second-order statistics. This has, however, motivated and allowed us to formulate and seek funding for

new studies to confirm if this finding is independent of other known predictor variables.

Future studies will investigate whether any related management strategies may help to optimize cerebral perfusion and improve functional outcome. In fact, it has been long recognized that changes in head and body posture can worsen or improve neurological symptoms in occlusive cerebrovascular disease by inducing changes in CBF [21, 22]. The potential mechanisms include a gravitational effect in passively dilated vessels due to impaired cerebral autoregulation, the cardiovascular and respiratory effects of the upright position (including a reduction of blood pressure), increased venous return, altered cardiac output and postural hypocapnia related to hyperventilation and improved chest wall compliance [23, 24]. Interestingly, it has been found that flat HOB positioning increases CBF possibly by improving the efficiency of passive-pressure dependent collateral flow [7, 25]. Thus, postural tilting has been proposed as a potential challenge for assessing and enhancing the functional capacity of collateral circulation [26].

The $\Delta rCBF_{30}$ was found to be paradoxical or reduced in patients with unfavorable outcome, where some patients did not respond to the HOB position change. The reason of this decreased $\Delta rCBF_{30}$ could be that these patients suffered from cerebral autoregulation impairment [27]. Recently, in non-stroke patients, Lam et al. studied the cerebral autoregulation, the critical closing pressure, the mean arterial pressure and the CBFV during a similar protocol [28]. As hypothesized before [29], the cerebral autoregulation remained intact after the HOB position change, but the critical closing pressure, the mean arterial pressure and the CBFV were decreased. CBFV changes were $-15.5 \pm 14.0\%$, which are similar to our results of patients with a favorable outcome [$\Delta rCBF_{30}$ of -10.4 (-12.7 , -7.3)% and -8.8 (-13.5 , -5.5)% for early and late].

The HOB position change as a stimulus to test the cerebrovascular reactivity is attractive, because, compared to other stimuli, it is non-invasive, easy to perform and does not require subject collaboration. As reported in previous studies in both brain injured and healthy subjects [3, 4, 8, 14–16], HOB angle manipulation was well tolerated and no changes in the stroke severity were observed.

The latest advances in DCS have provided a better insight into the behavior of CBF dynamics during these mentioned HOB changes by monitoring microvascular CBF in the frontal cortex at the bedside and without the need of an exogenous contrast [13]. In agreement with previous DCS studies [3, 4, 14], we have observed a substantial inter-individual variation in CBF responses to HOB changes. In contrast, a more homogeneous response to HOB manipulation among individuals has been described in healthy subjects [15]. This is consistent with the presence of different degrees of collateral flow and cerebral autoregulation impairment after

AIS. Unfortunately, in our study no collateral scores have been assessed.

We acknowledge that our study has several limitations. First, the high admission NIHSS score limited our findings to patients with large hemispheric strokes. Another limitation is technological, DCS measures information from the cortical brain, but partly it also contains scalp and skull contributions. We did not take any measures to account for this but relied on previous validation studies [13]. Finally, our recruitment at the early phase was limited, which should be improved in the future with the recent emergence of commercial user-friendly systems (e.g., HemoPhotonics S.L. and ISS). An intervention randomized controlled study is underway to determine whether CBF variation during position changes is a risk factor or only a biomarker of worse functional outcome.

In conclusion, microvascular CBF response to an increase of the HOB during the early phase of stroke has been related to the outcome. The HOB response could be related to the functional capacity of collateral circulation. However, further studies are needed to elucidate if this information could be used to individualize management for the patients in the Stroke Unit for improving the functional outcome after AIS.

Funding This work was funded by Redes Temáticas de Investigación Cooperativa (RETICS-INVICTUS RD012/0014, RD16/0019/0010), Fundació CELLEX Barcelona, Ministerio de Economía y Competitividad/FEDER (PHOTODEMENTIA, DPI2015-64358-C2-1-R), ISCIII/FEDER (MEDPHOTAGE, DTS16/00087, FIS-PI09/0557, FIS2015-71851-P), “Severo Ochoa” Programme (SEV-2015-0522), Obra Social “la Caixa” (LlumMedBcn, Recerca Matemàtica Col·laborativa), Institució Centres de Recerca de Catalunya, Agència de Gestió d’Ajuts Universitaris i de Recerca (2017SGR-1380, 2014SGR-1307), LASER-LAB-EUROPE IV (EU-H2020-654148), Whitaker International, T32 HL007954 Multidisciplinary training in cardiovascular biology, “Fundació La Marató TV3” (201709.31) and Marie Curie Initial Training Network (OILTEBIA/317526).

Compliance with standards

Conflicts of interest ICFO has equity ownership in HemoPhotonics S.L. commercializing relevant technologies. Potential financial conflicts of interest and objectivity of research have been monitored by ICFO Knowledge & Technology Transfer Department and none were identified.

Ethical standard All human studies have been approved by the appropriate ethics committee (EC/15/130) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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