ORIGINAL ARTICLE

Cerebral autoregulatory performance and the cerebrovascular response to head-of-bed positioning in acute ischaemic stroke

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Background and purpose: Cerebrovascular responses to head-of-bed positioning in patients with acute ischaemic stroke are heterogeneous, questioning the applicability of general recommendations on head positioning. Cerebral autoregulation is impaired to various extents after acute stroke, although it is unknown whether this affects cerebral perfusion during posture change. We aimed to elucidate whether the cerebrovascular response to head position manipulation depends on autoregulatory performance in patients with ischaemic stroke.

Methods: The responses of bilateral transcranial Doppler ultrasound-determined cerebral blood flow velocity (CBFV) and local cerebral blood volume (CBV), assessed by near-infrared spectroscopy of total hemoglobin tissue concentration ([total Hb]), to head-of-bed lowering from 30° to 0° were determined in 39 patients with acute ischaemic stroke and 17 reference subjects from two centers. Cerebrovascular autoregulatory performance was expressed as the phase difference of the arterial pressure-to-CBFV transfer function.

Results: Following head-of-bed lowering, CBV increased in the reference subjects only ([total Hb]: + 2.1 ± 2.0 vs. + 0.4 ± 2.6 μM; $P < 0.05$), whereas CBFV did not change in either group. CBV increased upon head-of-bed lowering in the hemispheres of patients with autoregulatory performance <50th percentile compared with a decrease in the hemispheres of patients with better autoregulatory performance ([total Hb]: +1.0 ± 1.3 vs. −0.5 ± 1.0 μM; $P < 0.05$). The CBV response was inversely related to autoregulatory performance ($r = -0.68$; $P < 0.001$) in the patients, whereas no such relation was observed for CBFV.

Conclusion: This study is the first to provide evidence that cerebral autoregulatory performance in patients with acute ischaemic stroke affects the cerebrovascular response to changes in the position of the head.

Introduction

Ischaemic stroke results from a serious mismatch between oxygen demand and delivery due to a sudden interruption in the blood supply to the affected brain region. Neurons located in the ischaemic core of the infarction are generally not eligible for recovery, whereas neurons in the penumbra have the potential

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to regain function, provided that a sufficient recovery of blood supply and tissue oxygenation occurs [1]. Cerebral perfusion pressure decreases when the brain is elevated above heart level [2], which is potentially of importance for patient positioning and mobilization after a stroke [3]. However, at group level, a horizontal versus elevated head-of-bed position for the first 24 h after stroke does not seem to affect neurological outcome [4]. On the other hand, the cerebrovascular effect of head-of-bed positioning in acute ischaemic stroke is quite heterogeneous, including paradoxical responses [5–12]. This questions generalized recommendations and suggests that patient-tailored positioning may be more appropriate.

Cerebral blood flow (CBF) is autoregulated, i.e. it is maintained more or less constant despite changes in cerebral perfusion pressure [13]. Acute ischaemic stroke negatively affects cerebral autoregulatory performance [14–16]. The dependency of cerebral perfusion on head-of-bed position in patients with stroke has been suggested to reflect impaired autoregulation [5,9,12], but whether autoregulation performance impacts on the cerebrovascular response to changes in head-of-bed position has not been substantiated.

We hypothesized that the cerebrovascular response to head-of-bed manipulation depends on cerebral autoregulatory performance in acute ischaemic stroke. We aimed to determine the relationship between cerebral autoregulatory performance and the cerebrovascular response determined by transcranial Doppler (TCD) ultrasonography and near-infrared spectroscopy (NIRS) to head-of-bed lowering in patients with acute ischaemic stroke and in reference subjects.

Methods

Subjects

Consecutive patients admitted to the Stroke Units of the Academic Medical Centre (Amsterdam, The Netherlands) and Bispebjerg Hospital (Copenhagen, Denmark) with an acute onset of non-convulsive focal neurological deficit were included. Exclusion criteria were signs of cerebral hemorrhage on computed tomography scan, arrhythmia, a history of cardiac or central nervous system disease or inability to provide informed consent. Stroke severity was quantified according to the National Institutes of Health Stroke Scale. Age-matched volunteers without a history of cardiac or central nervous system disease served as reference subjects. Subjects received verbal and written explanation about the objectives and measurement techniques associated with the study. Informed consent was provided in accordance with the Helsinki Declaration. The Medical Ethics committees of the Academic Medical Centre and Bispebjerg Hospital approved the study protocol.

Protocol and measurements

Bedside measurements were performed at the stroke units <48 h after onset of stroke. Reference subjects were studied ≥2 h after a light meal without caffeine-containing beverages. Instrumentation was performed with the head-of-bed position elevated to 30°. Subsequently, a 5-min baseline measurement in the same position was followed by 0° head-of-bed position for 5 min. In all patients (n = 39) and reference subjects (n = 17) continuous blood pressure was measured (Portapres M2; TNO-BMI, Amsterdam, The Netherlands) with the cuff applied to the midphalanx of the middle finger of the non-paralytic hand fixed at heart level and calibrated by oscillometry (M5-I; Omron Healthcare Inc., Kyoto, Japan). To estimate CBF, bilateral blood flow velocity was measured by TCD ultrasonography (Multidop ×4; DWL, Singen, Germany) through the temporal acoustic windows in the proximal segments of the left and right middle cerebral artery. TCD ultrasonography determines cerebral blood flow velocity (CBFV) in large cerebral arteries leaving changes in microvascular and collateral blood flow undetected. In patients and reference subjects from Amsterdam, bilateral changes in the cerebral microcirculation were monitored using continuous-wave NIRS (Oxymon Mk II; Artinis Medical Systems BV, Elst, The Netherlands). NIRS tracks microvascular perfusion by trans-illuminating the cerebral cortex and detects head-of-bed position-induced changes in cerebral perfusion not sensed by TCD ultrasonography [5,6,12,17]. NIRS differentiates between oxygenated ([oxy-Hb]) and deoxygenated ([deoxy-Hb]) hemoglobin tissue concentration, with local changes in cerebral blood volume (CBV) being reflected by total hemoglobin tissue concentration ([total Hb]) [18–20]. During manipulation of CBF, [oxy-Hb] runs in parallel with the brain capillary oxygen saturation [21] and relates to the blood-oxygen-level-dependent functional magnetic resonance imaging [22–25]. A differential path length factor of 6.0 was applied to account for the scattering of light in the tissue. NIRS signals were recorded at 10 Hz above the supraorbital ridge and below the hairline. Changes in cutaneous perfusion may interfere with the accuracy of cerebral oximetry, whereas the distance between the transmitter and the receivers was 5.5 cm to assure sufficiently deep penetration of the near-infrared light into the brain to exclude substantial contamination from the extracerebral circulation [18]. TCD ultrasonography probes and

NIRS optodes were secured with a headband (modified Mark 600; Spencer Technologies, Redmond, WA, USA). Blood pressure, TCD ultrasonography and NIRS signals were analog-to-digital converted and stored for analysis.

Analysis

Changes in [oxy-Hb], [deoxy-Hb] and [total Hb] were expressed relative to baseline (30° head-of-bed position). Mean arterial pressure (MAP) and CBFV were the integral over one heartbeat. Heart rate was taken from the pressure pulse interval. MAP_{brain} accounted for the hydrostatic difference between the level of the heart and the TCD ultrasonography probe at 30° head-of-bed elevation. Cardiac stroke volume was determined by pulse wave analysis (BeatScope 1.0 software; BMEYE, Amsterdam, The Netherlands) and cardiac output was cardiac stroke volume × heart rate.

Cerebral autoregulatory performance in dampening the transfer of fluctuations in arterial pressure to CBFV can be represented by the latency between the input (arterial pressure) and output (CBFV) signals. To that purpose, cerebral autoregulatory performance was assessed in the frequency domain in order to determine the phase difference (Φ) between MAP and CBFV, where lower Φ implies more passive following of CBFV to fluctuations in arterial pressure and hence reduced cerebral autoregulatory performance [14,15,26]. A 4-min tracing of beat-to-beat data of MAP and CBFV was spline interpolated and resampled at 4 Hz. To quantify the variability of MAP and CBFV, their power spectra were determined by transforming the MAP and CBFV time series with discrete Fourier transformation to the frequency domain. Transfer function phase difference (Φ) and gain were derived from the cross spectrum. According to the high-pass filter model of cerebral autoregulation (CA) performance, performance of autoregulation is reflected by the Φ between oscillations of MAP (input function) and CBFV (output function) [27,28]. Results were expressed as the averaged integrated area for the low (0.07–0.15-Hz) frequency range. The transfer function gain was normalized for MAP and CBFV and expressed as the percentage change in CBFV per percent change in MAP to account for intersubject variability [14,15]. To examine the strength of the relationship between MAP and CBFV, coherence was used to express the degree to which the two signals co-vary significantly. Coherence above 0.5 was considered to provide a reliable estimate of the transfer function variables [28].

Differences between hemispheres and between head-of-bed positions were examined by two-way ANOVA for repeated measurements. Comparison between hemispheres with high versus low cerebral autoregulatory performance was performed after dichotomizing data according to the median Φ for each group. Differences between patients and reference subjects were identified by *T*-test when data fit a normal distribution; otherwise, Mann–Whitney *U*-test was used. Data of the left and right hemispheres in the reference subjects were averaged. Correlation between the cerebrovascular responses to head-of-bed lowering and cerebral autoregulatory performance was evaluated by univariate linear regression analysis. Data are presented as mean ± SD unless otherwise indicated. $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 39 patients with acute ischaemic stroke met the inclusion criteria and 17 healthy volunteers served as reference subjects (Table 1). Figure 1 summarizes patient eligibility and inclusion according to data quality and availability. All recordings from the reference subjects fulfilled the required signal quality for analysis; MAP–CBFV coherence was insufficient for determination of cerebral autoregulatory performance in one patient hemisphere.

Table 1 Demographics of patients and reference subjects

	Patients with stroke	Reference subjects
Male/female	20/19	7/10
Age (years)	68 ± 12	64 ± 7
Weight (kg)	75 ± 15	72 ± 11
Height (cm)	173 ± 9	169 ± 8
BMI	25 ± 4	26 ± 4
Stroke side (R/L)	20/19	N/A
NIHSS score	8 ± 6	N/A
History		
Hypertension	11	2
Diabetes mellitus	3	0
Dyslipidemia	5	2
Medication		
β-blocker	9	2
ACE inhibitor	2	1
AT_2RA	4	2
Diuretic	7	0
Cholesterol-lowering drug	12	2
Glucose-lowering drug	2	0

Data are given as mean ± SD. ACE, angiotensin-converting enzyme; AT_2RA, angiotensin type 2 receptor antagonist; BMI, body mass index; L, left; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; R, right.

Cerebrovascular autoregulation and cerebrovascular responses to head-of-bed lowering

Autoregulatory performance was not significantly different between groups or hemispheres (Table 2). In response to head-of-bed lowering, local CBV, reflected by NIRS-determined [total Hb], increased in the hemispheres of patients with autoregulatory performance <50th percentile ($\Phi < 37°$), whereas it tended to decrease in the hemispheres of patients with better autoregulatory performance (Fig. 2). The local CBV responses to head-of-bed lowering related inversely to Φ in the patients ($P < 0.05$) (Fig. 3), whereas no such relationship was found in the reference subjects (Fig. 3). In both groups, the TCD ultrasonography determined that CBFV response to head-of-bed lowering did not relate to autoregulatory performance.

Cardiovascular and cerebrovascular responses to head-of-bed lowering

At baseline with the head-of-bed position elevated at 30°, MAP, heart rate and cardiac output were higher in the patients, whereas CBFV was similar in patients and reference subjects (Fig. 4). In both groups, head-of-bed lowering increased MAP_{brain} and cardiac output but not CBFV. Local CBV increased in the reference subjects only, mainly as a result of an increase in [oxy-Hb], whereas changes in the patients were non-significant at group level (Fig. 4).

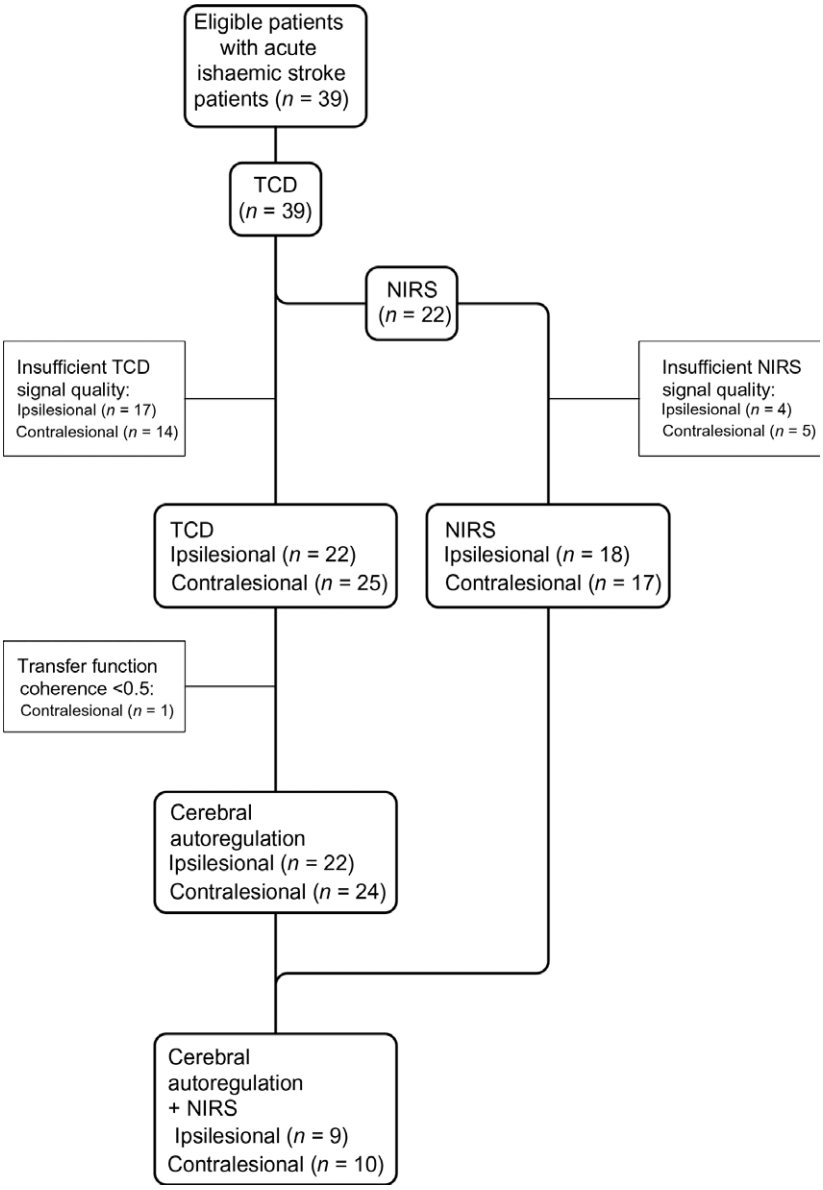

Figure 1 Inclusion and assessment of near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) ultrasonography in ipsilateral and contralateral hemispheres in patients with stroke.

Table 2 Dynamic cerebral autoregulation

	Stroke		Reference group
	Ipsilateral	Contralateral	
MAP power ($mmHg^2/Hz$)	6.3 ± 3.8[a]		3.8 ± 2.9
CBFV power[$(cm/s)^2/Hz$]	3.1 ± 2.8	4.6 ± 8.6	2.5 ± 2.3
MAP–CBFV transfer function			
Φ (°)	43 ± 18	48 ± 21	42 ± 11
Normalized gain (%/%)	0.37 ± 0.20	0.47 ± 0.49	0.53 ± 0.31
Coherence (k^2)	0.71 ± 0.13	0.69 ± 0.15	0.74 ± 0.09

Data are given as mean ± SD. Φ, phase difference; CBFV, cerebral blood flow velocity; MAP, mean arterial pressure. [a]$P < 0.01$ vs. reference group.

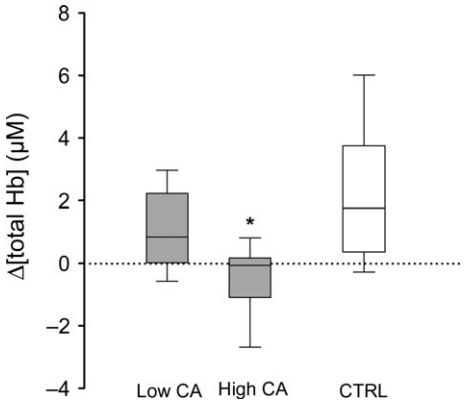

Figure 2 Changes in cerebral blood volume, expressed as cerebral total hemoglobin tissue concentration (Δ[total Hb]), after head-of-bed lowering in hemispheres with cerebral autoregulation (CA) performance <50th percentile vs. >50th percentile (Φ = 37°) in patients with acute stroke (■) and reference subjects (□). Boxes indicate median, 25th and 75th percentile, error bars indicate 10th and 90th percentile. CTRL, control. *$P < 0.05$ vs. lower CA performance.

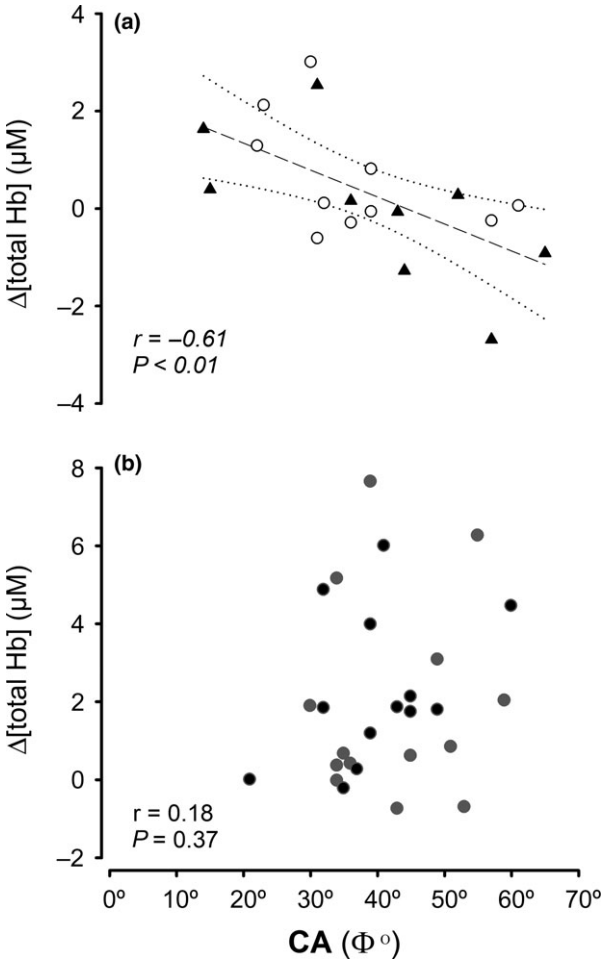

Figure 3 Relation between cerebral autoregulation (CA) performance and the change in cerebral total hemoglobin tissue concentration [total Hb] after head-of-bed lowering in patients with stroke (a) (▲, affected hemispheres; ○, non-affected hemispheres) and reference subjects (b) (●, left hemispheres; ●, right hemispheres).

Discussion

The cerebrovascular response to head-of-bed positioning in acute ischaemic stroke varies widely across patients [5–12]. In the present study, we reveal that, in patients with acute ischaemic stroke, the cerebrovascular response to a change in head position relates to cerebral autoregulatory performance. This is of clinical relevance considering the potential influence of positioning and mobilization on clinical outcome in ischaemic stroke [3]. The data suggest that cerebral autoregulatory performance is to be accounted for when considering patient head positioning and mobilization.

Transcranial Doppler ultrasonography tracks blood flow velocity in large vessels and constancy of the insonated vessel diameter, as assessed with ultra-high-field magnetic resonance imaging, links velocity to flow [29], rather than reflecting collateral perfusion in patients with cerebrovascular disease [5]. Within the cortical volume sampled by NIRS, hemoglobin is contained in arterioles, capillaries and venules, whereas the relative arterial and venous contributions vary [30] and changes in [total Hb] correspond to CBV determined by positron emission tomography [19,20]. Combining TCD ultrasonography and NIRS provides insight into the perfusion changes in both large and small cerebral blood vessels, including collateral circulation [5,6]. The requirement for adequate signal quality together with sufficient transfer function coherence limited the number of observations in which we were able to relate the cerebrovascular to the cerebral autoregulatory performance. In particular, obtaining

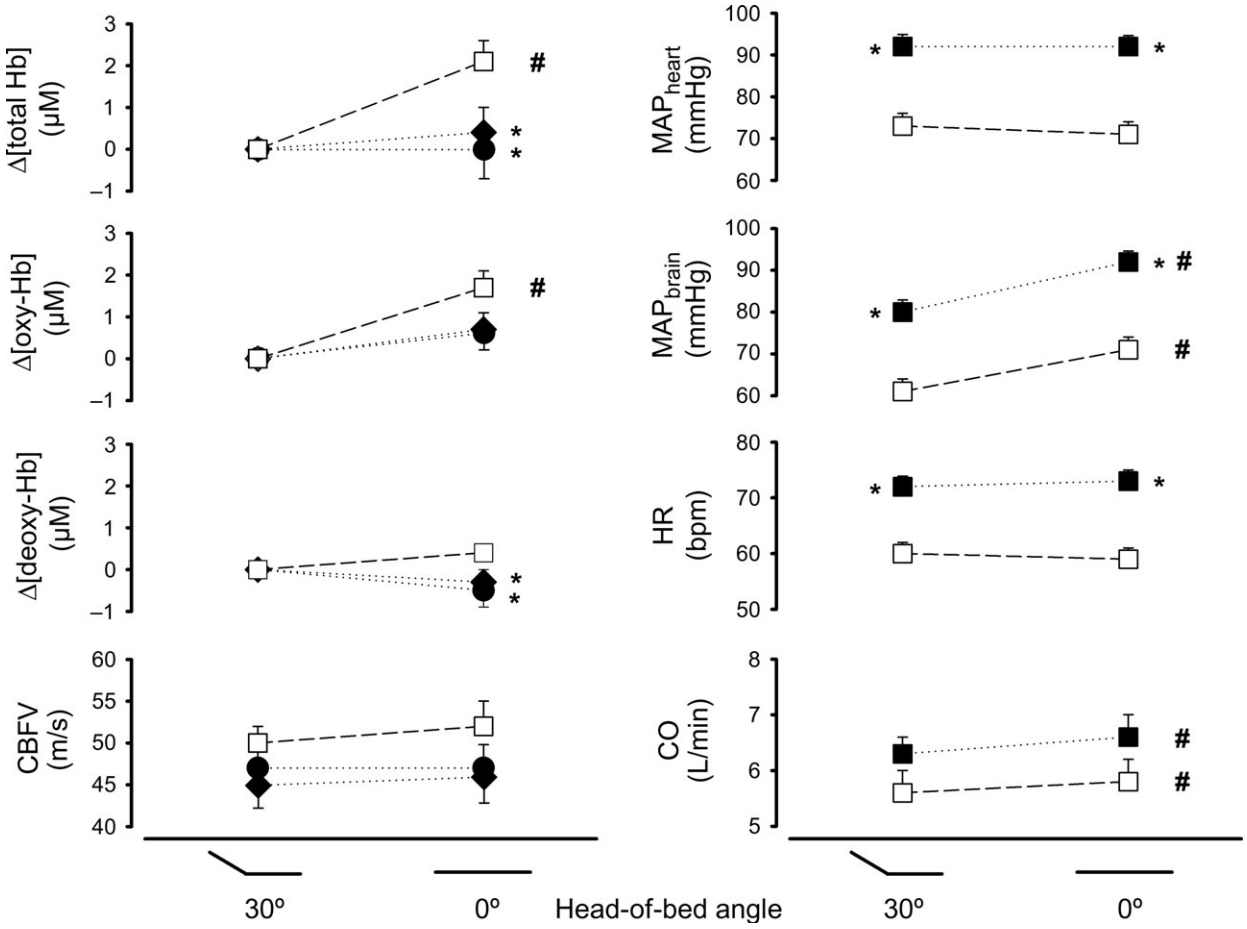

Figure 4 Cardiovascular and cerebrovascular variables during head-of-bed position lowering in patients (■) [ipsilateral (♦) and contralateral ● hemispheres] and control subjects (□). Δ[total Hb], change in total hemoglobin tissue concentration; Δ[oxy-Hb], change in oxygenated hemoglobin tissue concentration; Δ[deoxy-Hb], change in deoxygenated hemoglobin tissue concentration; CBFV, cerebral blood flow velocity; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure. Near-infrared spectroscopy data are relative changes to 30°. $*P < 0.05$ vs. control; $\#P < 0.05$ vs. 30°. Data are mean ± standard error.

good-quality TCD ultrasonography data can be challenging, illustrated by a study in more than 3000 (healthy) subjects where bilateral TCD ultrasonography signals were available in <50% of subjects [31]. Nevertheless, the present study is the first to demonstrate a relation between cerebral autoregulatory performance and the cerebrovascular response to head positioning in acute ischaemic stroke.

Initial observations in patients with severe ischaemic stroke suggested CBF as being maximal in the horizontal head-of-bed position [9,10], but this was not unanimously confirmed in more recent studies in mild to moderate stroke [5–7]. Considerable heterogeneity in responses has been observed ranging from an increase to indifferent or paradoxical reactions that could not be explained by clinical or radiological patient features [5–8,11]. Our findings are not intended to support either the horizontal or elevated head-of-bed position as it remains uncertain how these physiological effects translate into clinical outcome. Recently, the lying-flat position versus the sitting-up position for the first 24 h after stroke did not affect neurological outcome at group level [4]. However, very early mobilization versus standard care in patients with stroke resulted in a less favorable outcome [3], whereas the role of cerebral perfusion in this outcome is as yet unknown.

Fundamentally, CA is an abstract entity rather than a physical quantity [28], with autoregulatory performance as a continuum of stages rather than an 'all-or-nothing' phenomenon. Cerebral autoregulatory performance is highly variable among both patients and healthy subjects [14–16] and clear cut-off criteria on 'normal' versus 'impaired' autoregulation are as yet lacking [26]. CA counter-regulates an increase in cerebral perfusion pressure by means of cerebral vasoconstriction reducing CBV [32]. However, cerebral hypoperfusion and ischaemia induce compensatory

cerebrovascular vasodilatation until autoregulatory capacity becomes exhausted with increased CBV [33]. Local increases in CBV induce pressure differentials potentially provoking brain tissue shifts and neurologic deterioration [34]. Less effective CA in ischaemic stroke is associated with an increased risk of cerebral edema and hemorrhagic transformation [33–35] and worse clinical outcome [36]. The ideal head-of-bed position after ischaemic stroke is to be balanced between optimal cerebral perfusion and minimal risk for cerebral edema, reperfusion injury, hemorrhagic transformation or respiratory complications [37].

Postural changes in cerebral perfusion are commonly considered to reflect impairment of CA in patients with stroke. However, in healthy humans, positional changes in cerebral perfusion are physiological with a ~15% postural reduction in CBV and ~8% postural reduction in cerebral cortical oxygenation [6,38–40]. Together with Aries *et al*. [6], the present study is one of few that included a reference group without manifest cerebrovascular disease. Although the average cerebral autoregulatory performance did not differ between the two groups, the increase in CBV with head-of-bed lowering in the reference subjects was larger and not related to cerebral autoregulatory performance. Aries *et al*. observed a similar trend toward larger cerebrovascular changes in healthy controls versus patients with stroke [6]. We may speculate that, according to the Monro–Kellie doctrine [41], CBV after ischaemic stroke could be less responsive to postural changes as cerebral edema and increased intracranial pressure avert the inflow of extra blood volume.

Conclusion

Our study provides evidence that, in patients with acute ischaemic stroke, cerebral autoregulatory performance affects the cerebrovascular response to changes in the position of the head. The findings suggest that patients could benefit from individualized positioning and mobilization and question the feasibility of generalized recommendations on this issue.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interests.

References

1. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke* 1981; **12**(6)**:** 723–725.
2. Rosner MJ, Coley IB. Cerebral perfusion pressure, intracranial pressure, and head elevation. *J Neurosurg* 1986; **65**(5)**:** 636–641.
3. Bernhardt J, Langhorne P, Lindley RI, *et al*. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015; **386**(9988)**:** 46–55.
4. Anderson CS, Arima H, Lavados P, *et al*. Cluster-randomized, crossover trial of head positioning in acute stroke. *N Engl J Med* 2017; **376**(25)**:** 2437–2447.
5. Favilla CG, Mesquita RC, Mullen M, *et al*. Optical bedside monitoring of cerebral blood flow in acute ischemic stroke patients during head-of-bed manipulation. *Stroke* 2014; **45**(5)**:** 1269–1274.
6. Aries MJ, Elting JW, Stewart R, De Keyser J, Kremer B, Vroomen P. Cerebral blood flow velocity changes during upright positioning in bed after acute stroke: an observational study. *BMJ Open* 2013; **3**(8)**:** e002960.
7. Hunter AJ, Snodgrass SJ, Quain D, Parsons MW, Levi CR. HOBOE (Head-of-Bed Optimization of Elevation) Study: association of higher angle with reduced cerebral blood flow velocity in acute ischemic stroke. *Phys Ther* 2011; **91**(10)**:** 1503–1512.
8. Busch DR, Gregori-Pla C, Blanco I, *et al*. Blood flow response to orthostatic challenges in health and diseased populations. *Clin Transl Biophotonics* 2016; TTh4B. 5.
9. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. *Stroke* 2002; **33**(2)**:** 497–501.
10. Wojner-Alexander AW, Garami Z, Chernyshev OY, Alexandrov AV. Heads down: flat positioning improves blood flow velocity in acute ischemic stroke. *Neurology* 2005; **64**(8)**:** 1354–1357.
11. Olavarria VV, Lavados PM, Munoz-Venturelli P, *et al*. Flat-head positioning increases cerebral blood flow in anterior circulation acute ischemic stroke. A cluster randomized phase IIb trial. *Int J Stroke* 2017; https://doi.org/10.1177/1747493017711943. [Epub ahead of print]
12. Durduran T, Zhou C, Edlow BL, *et al*. Transcranial optical monitoring of cerebrovascular hemodynamics in acute stroke patients. *Opt Express* 2009; **17**(5)**:** 3884–3902.
13. Lassen NA. Autoregulation of cerebral blood flow. *Circ Res* 1964; **15**(Suppl. 1)**:** 201–204.
14. Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis* 2003; **16**(1)**:** 69–75.
15. Immink RV, van Montfrans GA, Stam J, Karemaker JM, Diamant M, van Lieshout JJ. Dynamic cerebral autoregulation in acute lacunar and middle cerebral artery territory ischemic stroke. *Stroke* 2005; **36**(12)**:** 2595–2600.
16. Reinhard M, Roth M, Guschlbauer B, *et al*. Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke* 2005; **36:** 1691–1696.
17. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977; **198**(4323)**:** 1264–1267.
18. Claassen JA, Colier WN, Jansen RW. Reproducibility of cerebral blood volume measurements by near infrared spectroscopy in 16 healthy elderly subjects. *Physiol Meas* 2006; **27**(3)**:** 255–264.
19. Rostrup E, Law I, Pott FC, Ide K, Knudsen GM. Cerebral hemodynamics measured with simultaneous PET and near-infrared spectroscopy in humans. *Brain Res* 2002; **954**(2)**:** 183–193.
20. Ohmae E, Ouchi Y, Oda M, *et al*. Cerebral hemodynamics evaluation by near-infrared time-resolved spectroscopy: correlation with simultaneous positron emission tomography measurements. *NeuroImage* 2006; **29**(3)**:** 697–705.
21. Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, Gjedde A. Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J Cereb Blood Flow Metab* 2007; **27**(5)**:** 1082–1093.
22. Alderliesten T, De Vis JB, Lemmers PM, *et al*. Simultaneous quantitative assessment of cerebral physiology using respiratory-calibrated MRI and near-infrared spectroscopy in healthy adults. *NeuroImage* 2014; **85**(Pt 1)**:** 255–263.
23. Mehagnoul-Schipper DJ, van der Kallen BF, Colier WNJM, *et al*. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. *Hum Brain Mapp* 2002; **16**(1)**:** 14–23.
24. Kleinschmidt A, Obrig H, Requardt M, *et al*. Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *J Cereb Blood Flow Metab* 1996; **16**(5)**:** 817–826.
25. Huppert TJ, Hoge RD, Diamond SG, Franceschini MA, Boas DA. A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. *NeuroImage* 2006; **29**(2)**:** 368–382.
26. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB. Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab* 2016; **36**(4)**:** 665–680.
27. Diehl RR, Linden D, Lucke D, Berlit P. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. *Stroke* 1995; **26**(10)**:** 1801–1804.
28. Panerai RB. Assessment of cerebral pressure autoregulation in humans – a review of measurement methods. *Physiol Meas* 1998; **19**(3)**:** 305–338.
29. Verbree J, Bronzwaer AS, Ghariq E, *et al*. Assessment of middle cerebral artery diameter during hypocapnia and hypercapnia in humans using ultra-high-field MRI. *J Appl Physiol* 2014; **117**(10)**:** 1084–1089.
30. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology* 2000; **93**(4)**:** 947–953.
31. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Transcranial doppler hemodynamic parameters and risk of stroke: the Rotterdam study. *Stroke* 2007; **38**(9)**:** 2453–2458.
32. Grubb RL, Phelps ME, Raichle ME, Ter-Pogossian MM. The effects of arterial blood pressure on the

regional cerebral blood volume by X-ray fluorescence. *Stroke* 1973; **4**(3)**:** 390–399.
33. Derdeyn CP, Videen TO, Yundt KD, *et al*. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. *Brain* 2002; **125**(Pt 3)**:** 595–607.
34. Frank JI. Large hemispheric infarction, deterioration, and intracranial pressure. *Neurology* 1995; **45**(7)**:** 1286–1290.
35. Castro P, Azevedo E, Serrador J, Rocha I, Sorond F. Hemorrhagic transformation and cerebral edema in acute ischemic stroke: link to cerebral autoregulation. *J Neurol Sci* 2017; **372:** 256–261.
36. Reinhard M, Gerds TA, Grabiak D, *et al*. Cerebral dysautoregulation and the risk of ischemic events in occlusive carotid artery disease. *J Neurol* 2008; **255**(8)**:** 1182–1189.
37. Khatri R, McKinney AM, Swenson B, Janardhan V. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. *Neurology* 2012; **79**(13 Suppl. 1)**:** S52–S57.
38. Van Lieshout JJ, Pott F, Madsen PL, van Goudoever J, Secher NH. Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* 2001; **32**(7)**:** 1546–1551.
39. Kim YS, Nur E, van Beers EJ, *et al*. Dynamic cerebral autoregulation in homozygous Sickle cell disease. *Stroke* 2009; **40**(3)**:** 808–814.
40. Levine BD, Giller CA, Lane LD, Buckey JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation* 1994; **90**(1)**:** 298–306.
41. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology* 2001; **56**(12)**:** 1746–1748.