Flat-head positioning increases cerebral blood flow in anterior circulation acute ischemic stroke. A cluster randomized phase IIb trial.

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Title:

Flat-head positioning increases cerebral blood flow in anterior circulation acute ischemic stroke. A cluster randomized phase IIb trial.

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Abstract

Background. Whether lying-flat improves blood flow in patients with acute ischemic stroke (AIS) is unknown. Our aim was to investigate if lying-flat 'changes' cerebral blood flow velocities (CBFV) assessed by transcranial Doppler (TCD) in AIS patients.

Methods. In a multicenter cluster clinical trial, we randomly assigned patients within 12 hours from onset of a neurological deficit due to cerebral ischemia of the anterior circulation to lying-flat or upright head positioning. The primary outcome was a change of 8cm/sec or more in mean CBFV on TCD to the middle cerebral artery at 1 and 24 hours post-randomization, adjusted for imbalance in baseline variables. Secondary outcomes included serious adverse events (SAEs) and physical functioning at 90 days.

Results. Ninety-four of 304 patients screened were recruited. The primary outcome occurred in 11 (26%) of 43 patients in the lying-flat group and in 6 (12%) of 51 in the upright group at 1 hour (adjusted odds ratio, 3.81; 95% CI, 1.07 to 13.54), and in 23 (53%) and 18 (36%) patients in these respective groups at 24 hours (adjusted odds ratio, 3.04; 95% CI, 1.08 to 8.53). There were no between-group differences in SAEs, including pneumonia, heart failure or mortality, nor in functional outcome at three months (adjusted common odds ratio, 1.38; 95% CI 0.64 to 3.00).

Conclusion. The lying-flat head position was associated with a significant increase in CBFV at one and 24 hours within the ipsilateral hemisphere of anterior circulation AIS, without serious safety concerns.

Clinical trial registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT01706094.

Introduction

Reperfusion therapy, medical with a lytic agent or mechanical clot retrieval, is the only proven treatment for acute ischemic stroke, but the approach is expensive and poorly accessed by the majority of patients in the world. Pharmacological and non-pharmacological blood pressure (BP) augmentation therapies are promising new treatments for acute ischemic stroke (AIS), which aim to improve cerebral blood flow to the ischemic penumbra through mechanisms that involve recruitment of collateral and leptomeningeal vessels.[1-4] A simple approach to increasing cerebral blood flow might be through tilting the head of patients with AIS into a 'lying-flat' (0°) head position as opposed to the standard sitting up (30º) nursing care that is used in many centers and countries, as recommended in clinical guidelines.[5-8] Several observational studies suggest that lying-flat improves cerebral blood flow velocity (CBFV) as measured by transcranial Doppler (TCD),[9] but these data are not conclusive[10] and there is variability among clinicians over the best strategy regarding head positioning in AIS.[11] The aim of this study was to determine whether the lying-flat head position within 12 hours of symptom onset, as compared to upright head position, improves CBFV on TCD to the middle cerebral artery (MCA) in patients with anterior cerebral circulation AIS.

Methods

Study design

This was an open, prospective, multicenter, international, cluster randomized, 'proof of concept' phase IIb controlled trial, with masked outcome assessment. Three centers from 2 countries participated. All received local ethics approval. The full study protocol has been published in detail previously.[12]

Eligibility

Inclusion criteria were: age ≥18 years, have a clinical diagnosis of anterior circulation AIS by brain imaging that excluded hemorrhage or other cause of neurological symptoms, could be safely positioned either lying-flat (0º) or upright (30º) position before 12 hours from symptom onset, have some degree of neurological impairment defined by a National Institutes of Health Stroke Scale (NIHSS) score ≥1 upon admission to hospital, uncertainty of the balance of benefits and harms of different head positioning within the first 24 hours of admission, and written informed consent obtained. Exclusion criteria were: having any contraindication to the lying-flat head position (e.g. active vomiting, pneumonia, uncontrolled heart failure), have a low potential for benefit from either change in head position, have a high probability of death within the next 48 hours, have a concomitant medical illness that would interfere with the outcome assessments and/or follow-up, have decompressive craniectomy, carotid endarterectomy or other early planned surgical procedure, and absence of appropriate sonographic temporal bone window for TCD.

Randomization and blinding

All eligible patients admitted during a given month were randomly assigned to either lying-flat (intervention) or upright (control) head position. Thus, clusters were months, not centers, which allowed stroke care teams to follow a monthly protocol without the need for frequent changing of position for individual patients. Randomization of head position by month was generated using the online program QuickCalcs,[13] balanced by center, and managed by the principal investigator (VO) who had no involvement in TCD or follow up of patients; this permitted appropriate balancing of the intervention among clusters and centers. TCD results were assessed centrally by masked experienced neurosonologists. Adjudication of serious adverse events (SAEs) and endpoints were performed centrally masking the intervention and following detailed

criteria. The 90-day assessment of modified Rankin Scale (mRS) was conducted locally by trained staff masked to the intervention and other clinical information.

Procedures

Interventions were two nursing stroke care protocols: (a) lying-flat head position or (b) upright head position. In (a), patients were positioned to 0° as soon as possible after the diagnosis of AIS was made by brain imaging, and this position is then maintained for the next 24 hours. Side-lying was recommended for prevention of aspiration. From 24 to 48 hours, patients were allowed to have their head raised slowly (to a maximum of 15°) and to ensure they did not have any alteration in their neurological condition (i.e. avoidance of a decline in Glasgow coma scale (GCS) scores of >1 point or an increase in NIHSS score of >4 points). After 48 hours, patients may have had their head elevated further to the standard 30° or more. In (b), patients were positioned with their head up to 30° or more as soon as possible after the diagnosis of AIS was confirmed on brain imaging and maintained this position for at least the next 48 hours. If there was a clear neurological deterioration, defined by a decline in GCS scores of 1 point or an increase in NIHSS of >4 points, the patient's position could be changed. In all patients, checks of their position were made hourly during 48 hours after the intervention. All participants were managed by a dedicated stroke team in an acute stroke unit, high dependency or intensive care unit. Brain imaging (Computerized Tomography and/or Magnetic Resonance Imaging, and TCD) was conducted according to standardized techniques at baseline and at later stages, according to local protocols. The following information was collected on admission: medical history, medications at time of admission, blood pressure (BP), heart rate (HR), and scores on the GCS and NIHSS, brain imaging findings to rule out hemorrhagic, mean CBFV and pulsatility indexes (Pin) by baseline TCD on both MCA with the patient in 30°, according to a standard

protocol. Additionally, data were collected on arterial obstruction/occlusion and presence of collaterals on the baseline TCD, as well as aspects of AIS management, including use of thrombolysis and/or thrombectomy and routine laboratory tests. Patients were assessed during the first 48 hours with the primary goal of ensuring adherence to the allocated head position. Accordingly, head positions were recorded hourly for the first 48 hours. If the patient´s position was changed (e.g. for rehabilitation or visit to the bathroom), the reason(s) and time spent off position was recorded. The following information was collected: mean CBFV and Pin on both MCA by TCD at 1 (±30 minutes) and 24 hours (±4 hours); BP, GCS and NIHSS scores at 24 hours; and dysphagia screening test according to local protocols. NIHSS scores, dependency assessed with the mRS, diagnosis of pneumonia or heart failure (if occurred), and the date of discharge from hospital (if this had occurred on or prior to day 7, or day of discharge/transfer to another hospital, if earlier). On 90±7 days, all surviving patients were evaluated, either through in-person or telephone interview, where the following information was recorded: dependency assessed with the mRS, use of secondary prevention medications, and the occurrence of any SAE.[14] For patients who had died prior to any of the above scheduled assessments, the time and documented cause of death was collected. All SAEs were recorded and additional details were requested for any supplementary information related to an SAE and its outcome.

TCD insonation protocol

Three hand-held TCD examinations were performed by experienced neurosonologists, initially at baseline (TCD-0) immediately after the diagnosis was made, with the participant positioned at 30° sitting-up, using a standard diagnostic protocol (details of the insonation protocol is outlined in the Supplementary Appendix).[15,16] Transtemporal TCD was repeated at 60±30 mins (TCD-1) and at 24±4 hours (TCD-2) after allocation

to the randomized head position. For TCD 1 and 2, measurements of the mean CBFV and Pin were obtained on the M1 segment of each MCA at a depth of 50 to 60 mm, at the same time as measurements of BP and HR. Ultrasonography results were adjudicated centrally by two other experienced neurosonologists (AB and PMV) who were masked to the intervention.

Outcomes

The main outcome was significant change in the mean CBFV in the ipsilateral side of the AIS, as assessed by TCD to the MCA at 1 and 24 hours after head positioning. Secondary outcomes were neurological status according to a shift in scores on the NIHSS at 7 days (or discharge if earlier), and functioning according to an ordinal shift in the distribution of scores on the mRS at 90 days. Safety outcomes were the proportion of SAEs, including of pre-specific episodes of pneumonia and congestive cardiac failure in the first 7 days, and any intracerebral hemorrhage (ICH) or death by 90 days. Feasibility of the intervention was defined as the proportion of patients who were able to maintain the position for ≥24 hours. Adjudication of SAEs was performed centrally by clinicians who were blind to the randomized intervention.

Statistical analysis

A sample size of 23 group clusters for each intervention (total 46 clusters; each with an average of 2 patients), assuming an intracluster correlation index of 0.037, was estimated to provide 90% power with a 5% level of significance to detect a clinically significant increase in CBFV (mean difference 8.3 [11.4] cm/s) between the lying-flat and upright groups.[9] All analyses were performed at the patient and cluster levels according to the intention-to-treat principle. The primary analysis compared the proportion of patients with a mean CBFV 'change' of ≥8 cm/s in the ipsilateral side at 1 hour and at 24 hours after positioning. We used 8 cm/sec as the cut-off point, based on

the results of our previous systematic review and meta-analysis quantifying the effect of head position on CBFV measured with TCD in patients with AIS. In this review, which included 57 patients from 4 prospective observational studies, we found that patients positioned lying-flat (0 degrees) had a mean increase of 8.31 cm/sec (95% confidence interval [CI] 5.34-11.28) compared to CBFV in those in the upright position (30 degrees)[9]. All analyses were adjusted for the following variables: baseline CBFV, age, NIHSS, use of thrombolysis (or mechanical thrombectomy), and site of vessel occlusion and presence of collateral flow identified on TCD. A per-protocol analysis was also conducted. Safety outcomes were analyzed without adjustment. All analyses were performed using random effect mixed models. Pre-specified subgroup analyses of the primary outcome included an interaction test to determine whether the effect of treatment differed significantly across categories for each subgroup, expressed as a P value for heterogeneity. The following pre-specified subgroups were: age < or ≥65 years; NIHSS scores <10 or ≥10, <7 or ≥7, and below and above the overall median; time from symptom onset to positioning of <6 versus ≥6 hours; baseline systolic BP below and above the overall mean; use of intravenous thrombolysis (or mechanical thrombectomy); evidence of vessel occlusion of collateral blood flow on TCD; and the time in randomized head position of < or ≥ 24 hours. The same analyses for change in CBFV and across pre-specified subgroups were performed for the contralateral side of the AIS. A post hoc multivariate analysis adding atrial fibrillation and congestive heart failure was performed. Data are reported as odds ratios (OR) and 95% CI. Conventional two-sided levels of statistical significance (α=0.05) were used. All analyses were undertaken using SAS software, version 9.3 (SAS Institute). More details of the statistical analysis have been previously published.[17]

Results

From January 1 2013 through July 31 2015, 94 patients of 304 screened were recruited from 3 centers in 2 countries (Figure 1), 43 allocated to the lying-flat and 51 to upright head positions. There were no significant differences in baseline and clinical characteristics between the groups, except for those in the upright position having more congestive cardiac failure, atrial fibrillation, and occlusions of the terminal carotid and those lying-flat having more MCA M1 segment occlusions (Table 1). The mean (±SD) age of participants was 72 (14) years and 28 (29.8%) were female; the median (IQR) NIHSS was 6 (3 to 12) points.

There were similar times to the commencement and duration of head positioning between groups: lying-flat, mean 5.5 (3.3) from symptom onset and median 45 (IQR 40 to 45) hours duration; upright, 5.0 (2.8) hours from symptom onset and median 44 (IQR 40 to 44) hours duration. Forty one patients (95%) and 50 (98%) maintained the allocated head position ≥24 hours in the lying-flat and upright positions, respectively (P=0.46). Baseline CBFV and BP were similar between the groups (Table 1 and Figure S1). There were no significant differences in the management between groups in hospital over the first 7 days, except for there being more use of antihypertensive drugs in those in the upright group (Table 1).

In adjusted analysis of the primary outcome, a mean change in CBFV of >8 cm/s in the ipsilateral side occurred in 11 patients (26%) allocated to the lying-flat head position and in 6 patients (12%) allocated to the upright head position at 1 hour (OR 3.81, 95% CI 1.07 to 13.54; P=0.04). At 24 hours, the primary outcome occurred 23 patients (53%) in the lying-flat position and 18 patients (36%) in the upright head position (OR 3.04, 95% CI 1.08 to 8.53; P=0.04). Overall adjusted mean difference in CBFV between groups was 6 cm/s (range 1.87 to 10.14; P=0.005) at 1 hour and 10.34 cm/s (-

1.7 to 22.38; P=0.09) at 24 hours (Table 2, Figure S2). Relative mean difference in CBFV in the ipsilateral side was 19.1% (95% CI 10.1 to 28.6; P<0.001) at 1 hour in the lying-flat compared to the upright head positions, and 26.1% (95% CI 11.5 to 44.0; P=0.002) at 24 hours (Table 2). Similar effects were evident in the per-protocol analysis (Table S1). In a post hoc multivariate analysis which included variables that could have produce selection bias due to orthopnea (CHF and AF) the results did not change (Table S2). Pin increased significantly at 1 and 24 hours in patients lying-flat in the contralateral side but not in the ipsilateral side, in the intention to treat population (Table S3).

There were no significant between-group differences in an ordinal analyses of the NIHSS at 7 days (Figure S2) and mRS at 90 days (adjusted common OR 1.38, 95% CI 0.64 to 3.0; P=0.42) (Figure 2).

There were no differences in the 90-day mortality between groups: 4 (9%) patients in the lying-flat and 3 (6%) in the upright positions (adjusted OR 5.78, 95% CI 0.66 to 50.2; P=0.12). There was no significant difference in occurrence of SAEs, including pneumonia and congestive cardiac failure between groups at 90 days (Table 3), although there were significantly more complaints of dorsal/lumbar pain in the lying-flat (12%) compared to upright (0%) head positions (P=0.01). There was no difference in other adverse events (Table S4).

Subgroup analysis in the intention-to-treat population showed consistency of treatment effect across pre-specified subgroups in the ipsilateral side at 1 and 24 hours (Figure 3). There were no significant differences in any of the other secondary outcomes including death or disability (mRS scores 3 to 6), early neurological deterioration, length of hospitalization, or ‘change’ in CBFV in the contralateral side (Table S5).

Discussion

This cluster clinical trial has shown that the lying-flat head position within 12 hours of symptom onset produced a significant large increase in CBFV as compared to the upright head position, in patients with mild/moderate AIS stroke involving the anterior circulation. These effects occurred within 1 hour of lying-flat but attenuated by 24 hours, in part from a late increase in CBFV in patients who adopted the upright position, as determined by serial TCD. Lying-flat was not associated with an increase in SAEs, although this position did produce some increase in back pain/discomfort in patients. The change in CBFV, however, did not translate into improved clinical outcomes for those in the lying-flat position at 7 or 90 days but the study was not powered for this purpose.

Our results confirm findings from previous observational non-randomized studies of there being an increase in CBFV in the ipsilateral but not contralateral side, from lying-flat in patients with AIS involving the territory of the MCA.[9,10]

One potential mechanism for the effect is gravitational force acting on passively dilated vessels to increase pressure gradients and residual blood flow in the ischemic brain, which is supported by the lack of change in Pin in the ipsilateral side and increase in the contralateral side in patients lying flat. Other explanations include improved collateral circulation to the ischemic penumbra region and passive vasodilatation of distal vessels from local perfusion pressure gradients.[18-20] The absence of any increase of CBFV on the contralateral side of cerebral infarction might relate to there being greater impairment of vasomotor reactivity in the region of ischemia/infarction.

There were low rates of aspiration pneumonia in our study, which may relate to the careful assessment and management of participants, including the use dysphagia screening protocols and appropriate feeding regimes, as well as the exclusion of high

risk patients such as those requiring intubation. However, similar low rates of pneumonia were recently reported in a retrospective study of consecutive unselected patients who were positioned in lying-flat after AIS.[21]

A key strength of this study was the use of cluster randomization to reduce potential contamination of the intervention between groups and improve fidelity of the protocol among clinical staff caring for patients. Another important strength of this study is the short time from symptom onset to commencement of positioning, which is in line with the proposed mechanism by which this intervention could have a clinically significant benefit, that of increasing cerebral blood flow to penumbral tissue. Other features were the blinded evaluation of CBFV and clinical outcomes, and the high agreement among neurosonologists performing TCD.[22]

There are some limitations, however, in that most participants were from a single center and there were imbalances in some of the baseline clinical characteristics related the overall small sample size. These aspects may have introduced bias, although the results were consistent in post-hoc adjusted analyses. Moreover, being a phase IIb clinical trial, these results may not apply to a broader range of patients, including those with posterior circulation or mild AIS, or with positioning introduced after 12 hours from symptom onset.

In summary, this cluster clinical trial of patients with anterior circulation AIS, showed that the lying-flat head position within 12 hours of symptom onset caused a significant increase in CBFV in the ipsilateral side of the lesion, without any serious safety concerns. Whether such head positioning translates into any clinical benefit within 24 hours of symptom onset in patients with stroke is being assessed in the phase 3 HeadPoST main study.[23]

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Contributors

AB, VVO, and PML designed the study. AB, PML, JG, PMV and FG acquired the data. All authors interpreted the data. HA did the statistical analysis with input from VVO and PML. VVO and PML wrote the first, and CSA wrote subsequent drafts, of the manuscript. All authors critically revised the draft and gave final approval for its publication. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the data.

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Figure legends

Figure 1: Flow diagram of patients.

Figure 2: Functional Outcomes at 90 Days, According to Score on the Modified Rankin Scale.

Figure 3: Subgroup analysis in the intention-to-treat population of the primary outcome defined as a significant change in cerebral blood flow velocity at 1 hour (A) and at 24 hours (B) of head positioning in the ipsilateral side of acute ischemic stroke, according to intervention group.

Table 1. Baseline characteristics of patients and management*

Variable	Lying-flat (N=43)	Upright (N=51)
Age, mean (SD), years	70 (14)	74 (14)
Female sex, no – (%)	10 (23)	18 (37)
Country of recruitment, no – (%)		
Australia	4 (9)	0 (0)
Chile	39 (91)	51 (100)
Medical history, no – (%)		
Hypertension	25 (58)	33 (65)
Previous stroke	11 (26)	13 (25)
Diabetes mellitus	7 (17)	9 (18)
Ischemic heart disease	9 (21)	14 (27)
Congestive heart failure†	2 (5)	10 (20)
Atrial fibrillation‡	5 (12)	16 (31)
Use of an antiplatelet agent	19 (44)	21 (41)
Use of lipid lowering therapy	16 (37)	19 (38)
Use of antihypertensive therapy	23 (53)	31 (61)
Use of oral anticoagulants	3 (7)	9 (18)
Systolic blood pressure, mean (SD), mmHg	151 (30)	148 (23)
Diastolic blood pressure, mean (SD), mmHg	85 (18)	83 (18)
Heart rate, mean (SD), bpm	74 (15)	72 (14)
NIHSS, median (IQR) §	6 (3 to 10)	7 (4 to 15)
NIHSS ≥10 (%)	11 (26)	20 (39)
NIHSS ≥7 (%)	17 (40)	26 (51)
Ipsilateral Site of occlusion		
Extracranial internal cerebral artery¶	4 (24)	0 (0)
Intracranial terminal internal carotid artery	1 (6)	1 (5)
Middle cerebral artery M1 segment ‖	5 (31)	14 (64)
Middle cerebral artery M2 segment	7 (41)	9 (41)
Anterior cerebral artery	1 (6)	0 (0)
Transcranial Doppler features, no – (%)		
Collateral blood flow		
Collaterals present	18 (42)	19 (37)
Occlusion detected	12 (28)	12 (24)
TIBI grade 0 (%)**	-	1 (2)
TIBI grade 1	2 (5)	2 (4)
TIBI grade 2	2 (5)	5 (10)
TIBI grade 3	9 (21)	6 (12)
TIBI grade 4	1 (2)	3 (6)
TIBI grade 5	29 (67)	34 (67)
Ipsilateral CBFV, mean (SD), cm/sec††	47.23 (17.29)	42.75 (17.15)
Contralateral CBFV, mean (SD), cm/sec††	54.86 (16.84)	47.02 (10.92)
Ipsilateral Pulsatility Index, mean (SD), cm/sec	1.02 (0.41)	1.04 (0.36)

Contralateral Pulsatility Index, mean (SD), cm/sec	0.95 (0.22)	0.99 (0.3)
Management		
Time from symptom onset to head positioning, mean (SD), hours	5.5 (3.3)	5.0 (2.8)
Time in allocated head position, median (iqr), hours	45 (40 to 45)	44 (40 to 46)
Dysphagia screening, no – (%)	40 (95)	48 (96)
Dysphagia present, no – (%)	4 (10)	6 (12)
Oral feeding, no – (%)	40 (95)	44 (90)
Enteral feeding, no – (%)	2 (5)	5 (10)
IV thrombolysis, no – (%)	27 (63)	27 (53)
Thrombectomy, no – (%)	3 (7)	7 (14)
Antiplatelets used, no – (%)	39 (95)	42 (84)
Statins used, no – (%)	41 (100)	46 (92)
Antihypertensives used, no – (%)*	10 (25)	27 (54)
Vasoactive drugs used, no – (%)	3 (7)	3 (6)
Antibiotics used, no – (%)	7 (17)	10 (21)
Intubation and ventilation, no – (%)	-	2 (4)

*Plus-minus are means ±SD. CI denotes confidence interval.
†P=0.03
‡P=0.02
§Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.
¶P=0.02
||P=0.05
**Thrombolysis in Brain Ischemia (TIBI) scores range from 0 to 5, with higher scores indicating completeness of recanalization.
†† cerebral blood flow velocity (CBFV)
* P=0.006

Table 2. Primary and secondary outcomes*

Outcomes	Lying-flat (N=43)	Upright (N=51)	Odds ratio (95% CI)	P value†
Primary				
CBFV change >8 cm/s on the ipsilateral side, -no. (%)‡				
At 1 hour	11 (26)	6 (12)	3.81 (1.07 to 13.54)	0.044
At 24 hours	23 (53)	18 (36)	3.04 (1.08 to 8.53)	0.04
Adjusted absolute CBFV difference, mean, cm/s§				
At 1 hour	5.49 (2.52 to 8.46)	-0.51 (-3.29 to 2.26)	6 (1.87 to 10.14)	0.005
At 24 hours	15.36 (6.63 to 24.09)	5.02 (-3.65 to 13.2)	10.34 (-1.7 to 22.38)	0.09
Adjusted relative CBFV difference, -no. (%)§				
At 1 hour	16.8 (9.4 to 24.7)	-2.2 (-8.1 to 4.1)	19.1 (10.1 to 28.6)	<0.001
At 24 hours	34.9 (22.1 to 48.9)	8.0 (-1.9 to 18.7)	26.1 (11.5 to 44.0)	0.002
Secondary				
NIHSS at 7 days — no. (%)¶			0.87 (0.38 to 1.98)	0.74
0 to 5, mild	36 (85)	39 (78)		
6 to 15, moderate	5 (10)	5 (10)		
16 to 42, severe	1 (3)	6 (12)		
Modified Rankin scale — no. (%)‖			1.38 (0.64 to 3.00)	0.416
0: No symptoms at all	13 (31)	11 (22)		
1: No substantive disability despite symptoms	15 (36)	13 (26)		
2: Slight disability	5 (12)	8 (16)		
3: Moderate disability requiring some help	4 (10)	5 (10)		
4: Moderate–severe disability requiring assistance	1 (2)	7 (14)		
5: Severe disability, bed-bound and incontinent	0 (0)	3 (6)		
6: Death	4 (10)	3 (6)		
Death and dependency**	9 (21)	18 (36)	0.71 (0.24 to 2.09)	0.54
Dependency at 90 days	5 (12)	15 (30)	0.35 (0.1 to 1.21)	0.103
Duration of hospitalization, mean (SD), days	9 (8)	13 (20)	2.4 (-5.0 to 9.8)	0.514

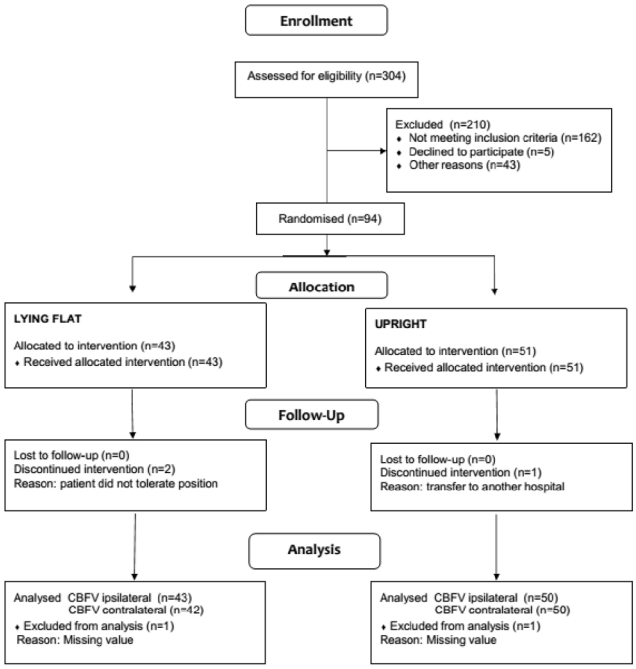
*Plus-minus are means ±SD. CI denotes confidence interval.
†P values are for the comparison of the lying-flat head position group with the upright head position group.
‡CBVF change was defined as >8 cm per second.
§Adjusted for baseline value of mean cerebral blood flow velocity, age, National Institutes of Health Stroke Scale (NIHSS) score, thrombolysis or thrombectomy performed, presence of collaterals and vessel occlusion present or not.
¶The common odds ratio was estimated from an ordinal logistic-regression model and indicates the odds of an increase of category in the NIHSS score, with a common odds ratio less than 1 favoring lying-flat head position.
||The common odds ratio was estimated from an ordinal logistic-regression model and indicates the odds of a decrease in score of 1 on the modified Rankin scale (mRS), with a common odds ratio greater than 1 favoring lying-flat head position.
**Dependency defined by a score of 3 to 5 on the mRS.

Table 3. Serious adverse events by groups in the per protocol population*

Variable	Lying-flat (N=41)	Upright (N=50)	Adjusted OR (95% CI)†	P value
Death at 90 days	4 (10)	3 (6)	6.04 (0.69 to 53.22)	0.11
Pneumonia at 7 days	0 (0)	1 (2)	-	-
Congestive heart failure at 7 days	0 (0)	0 (0)	-	-
Cerebral edema at 7 days	1 (3)	4 (9)	0.41 (0.02 to 10.09)	0.59
Hemorrhage on repeated brain imaging	2 (5)	7 (15)	0.43 (0.04 to 4.15)	0.47
Neurological deterioration at 7 days or death at 90 days	5 (12)	4 (8)	4.42 (0.72 to 26.98)	0.11
Recurrent stroke infarction at 90 days	2 (5)	3 (6)	0.71 (0.09 to 5.59)	0.75
Increased intracranial pressure with major deterioration	0 (0)	0 (0)	-	-
Increased intracranial pressure with minor deterioration	0 (0)	0 (0)	-	-

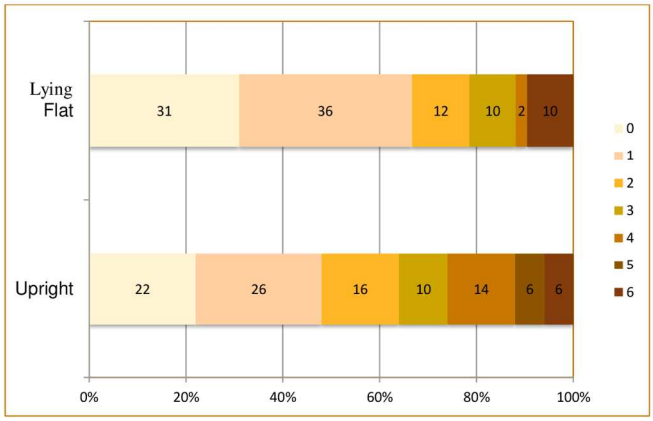
*CI denotes confidence interval, OR odds ratio.
†Adjusted for baseline value of mean cerebral blood flow velocity, age, National Institutes of Health Stroke Scale Score, thrombolysis or thrombectomy performed, presence of collaterals and vessel occlusion present or not.

Figure 1



Flow diagram of patients
Figure 1
215x279mm (200 x 200 DPI)

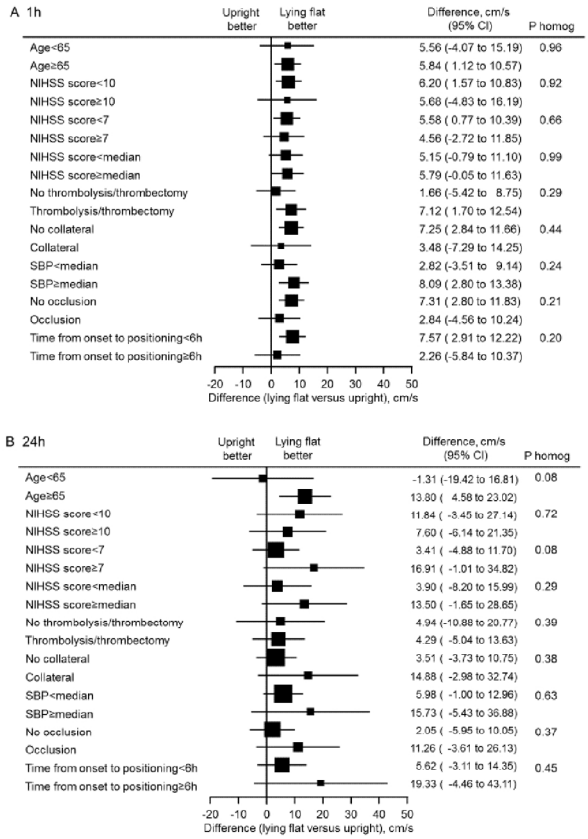
Figure 2



Shown is the raw distribution of scores on the modified Rankin scale at 90 days in the group that was positioned in the lying-flat head position and the group that was positioned in the upright head position. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

Functional Outcomes at 90 Days, According to Score on the Modified Rankin Scale.
Figure 2
215x279mm (200 x 200 DPI)

Figure 3



Subgroup analysis in the intention-to-treat population of the primary outcome defined as a significant change in cerebral blood flow velocity at 1 hour (A) and at 24 hours (B) of head positioning in the ipsilateral side of acute ischemic stroke, according to intervention group.

Figure 3

215x279mm (200 x 200 DPI)