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Review Article

Do acute stroke patients develop hypocapnia? A systematic review and meta-analysis

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ABSTRACT

Purpose: Carbon dioxide (CO_2) is a potent cerebral vasomotor agent. Despite reduction in CO_2 levels (hypocapnia) being described in several acute diseases, there is no clear data on baseline CO_2 values in acute stroke. The aim of the study was to systematically assess CO_2 levels in acute stroke. Material and methods: Four online databases, Web of Science, MEDLINE, EMBASE and CENTRAL, were searched for articles that described either partial pressure of arterial CO_2 ($PaCO_2$) and end-tidal CO_2 ($EtCO_2$) in acute stroke. Results: After screening, based on predefined inclusion and exclusion criteria, 20 studies were retained. There were 5 studies in intracerebral hemorrhage and 15 in ischemic stroke, totalling 660 stroke participants. Acute stroke was associated with a significant decrease in CO_2 levels compared to controls. Cerebral haemodynamic studies using transcranial Doppler ultrasonography demonstrated a significant reduction in cerebral blood flow velocities and cerebral autoregulation in acute stroke patients. Conclusion: The evidence from this review suggests that acute stroke patients are significantly more likely than controls to be hypocapnic, supporting the value of routine CO_2 assessment in the acute stroke setting. Further studies are required in order to evaluate the clinical impact of these findings.

1. Introduction

Changes in arterial partial pressure of carbon dioxide ($PaCO_2$) have a potent effect on the cerebral vasculature, demonstrated by a 4% flow change in the middle cerebral artery (MCA) for every 1 mmHg increase or decrease in $PaCO_2$ between the range of 20 to 80 mmHg [1,2]. Hypocapnic states, despite reducing cerebral blood flow (CBF), demonstrate the ability to widen the plateau region of the autoregulatory curve, thus improving autoregulatory capacity [3]. Therefore, hypocapnic states, may improve the inherent ability of the cerebrovasculature to keep CBF constant across changes in cerebral perfusion pressure. In disease states, like acute stroke, improving autoregulatory capacity may be clinically beneficial, particularly in the context of extremes of cerebral perfusion pressure from uncontrolled hypertension or rising intracranial pressures.

Despite recent advances in understanding the relationship between peripheral and central hemodynamic variables and $PaCO_2$ change in healthy volunteers [4], the carbon dioxide changes in acute stroke remain unclear. Observational studies have found lower than normal $PaCO_2$ in acute stroke patients [5] and no autoregulatory impairment. Could this be the consequence of the physiological effects of lower $PaCO_2$ on the cerebrovasculature in this population? Crucially, neuroprotective mechanisms in cerebrovascular disease highlight hypocapnia as a key mediator of lower intracranial pressures and restoration of penumbral areas around ischemic tissue [3]. However, these potential protective mechanisms are weighed against the risks of vasoconstriction-induced ischemia, as well as cerebral hyperemia associated with subsequent $PaCO_2$ normalisation [3].

International guidelines for the delivery of thrombectomy in acute stroke advocate use of capnography in acute ischemic stroke settings [6,7]. Furthermore, capnography has long had a role in several neurologically vulnerable states including cardiac arrest and seizure

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episodes. Increasingly, through observational [5] and interventional studies [8], we are understanding the relationship between $PaCO_2$ and CBF in acute stroke. However, there remains no clear data on baseline carbon dioxide values in acute stroke and whether hypocapnia exists post-stroke. End-tidal CO_2 ($ETCO_2$) is a surrogate measure of $PaCO_2$ and provides a non-invasive bed-side measurement tool for use in a ward-based setting. This systematic review and meta-analysis aims for the first time to determine if acute stroke patients tend to be hypocapnic, by assessment of studies incorporating carbon dioxide assessment in the acute stroke setting.

2. Material and methods

2.1. Study identification

The protocol implemented as part of this systematic review and meta-analysis was constructed using combined recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA [9], the check list results are presented in supplemental material Table I) and the Cochrane Handbook for Systematic Reviews.

2.2. Literature search strategy

Studies were identified with a search strategy across four English language databases (Web of Science, MEDLINE, EMBASE and CENTRAL), between 1966 and February 2019, accommodating different medical Subject Headings (MeSH) terms or subcategories available on each database (supplemental material Table II). Bibliographies of selected articles were screened for additional relevant articles. Disagreements were resolved through discussion with a third reviewer (RP).

2.3. Inclusion and exclusion criteria

Only studies in acute stroke that have monitored carbon dioxide levels were included. Eligibility was assessed by reading abstracts, and, if necessary, whole articles. The effects of carbon dioxide, CBF velocity (CBFV) changes (if applicable), cerebral autoregulation status (if applicable) and neurological outcome were assessed. Excluded were case reports, non-English language articles, posterior territory stroke studies, and studies with ultrasound contrast agent injection. The rationale for exclusion of studies focusing on posterior circulatory strokes was largely due to prior work demonstrating an inability to reliably assess the posterior territory as compared to the anterior territory in dynamic haemodynamic studies [10]. Studies using US contrast agents were excluded as there are concerns around the validity of indices associated with this procedure with issues raised including the low resolution and nonlinear relationship with blood pressure [11].

2.4. Data extraction

A standardized data extraction was used by two investigators (JM and AS) and checked by the other authors. Any discrepancies were settled by consensus. The following data were extracted: (1) stroke type; (2) stroke classification; (3) stroke severity on admission and assessment (NIHSS); (4) number of patients and controls; (5) breakdown of numbers by sex; (6) acute (< 48 h) vs. sub-acute (> 48 h) assessment; (7) method of data analysis: technique and signal processing method; (8) neurological outcome; (9) presence, timing and conclusion of follow-up studies; (10) duration of recordings; (11) status of cerebral autoregulation contralateral and ipsilateral; (12) CBFV values; (13) CO_2 values; (14) respiratory rate; (15) heart rate; (16) blood pressure (BP) values, and (17) main conclusions and results. The methodological quality of the selected studies was assessed by the Newcastle–Ottawa scale (NOS) for observational studies. This scoring system evaluates the quality of an article based on 3 broad perspectives: the cohort selection (0–4 points), comparability (0–2 points), and assessment of outcomes (0–3 points). A score of ≥ 7 points was suggestive of a high-quality study. Two independent reviewers (ASMS and JSM) undertook the methodological quality screening and data extraction of the included studies. Any discrepancies were settled by consensus.

2.5. Statistical analysis

All studies assessing $ETCO_2$ in acute strokes were included, however only those that also recruited controls were included in the meta-analysis (as opposed to descriptive review). The outcomes of interest were all continuous variables, so the weighted mean difference (wMD) with its corresponding 95% confidence interval (CI) for each parameter was computed in acute stroke and healthy controls. The software used for meta-analysis was Review Manager 5.3 (RevMan 5) provided by the Cochrane Library. The heterogeneity assumption was checked by the $\chi 2$-based Q test. An I^2 value of $> 50\%$ or a P value of < 0.05 for the Q_2 statistic indicated significant heterogeneity. In the presence of statistical heterogeneity, random-effects model was chosen for the computation of wMD with its corresponding 95%CI. Otherwise, no obvious heterogeneity was considered to have occurred in the included studies, and the fixed-effects model was selected to generate the wMD with its corresponding 95%CI. A wMD > 1 indicates that acute stroke is associated with higher parameters levels, whereas a wMD < 1 indicates that stroke is associated with a lower levels as compared to controls. The pooled and stratified (AIS and ICH) forest plot for each parameter was constructed to illustrate the weight ratio of each incorporated study. Random effects weighted meta-regression was used to evaluate the association between calculated effect size and potential confounder variables. The following covariates were tested: age, sex, blood pressure (BP), admission and assessment NIHSS, CA (TFA methods), and affected hemisphere (AH) and unaffected hemisphere (UH) CBFV. Meta-regression was not used for CA (ARI method) and assessment NIHSS due to the small number of studies included. We regressed one variable at a time. Significance level was established at $p < .05$. All meta-regression analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, U.S.A.).

3. Results

3.1. Summary of included studies

A detailed flow diagram of study selection is shown in Fig. 1. Eighteen thousand, seven hundred and eighty publications met the search criteria and were evaluated. After removing duplicates, we screened 18,322 articles, of which we removed 17,869 after title screening. The commonest reasons for exclusion were the inclusion of subarachnoid hemorrhage (9624 articles) or neonatal/child patients (5502 articles). After screening 453 abstracts, 24 articles were retained for full-text analysis. Overall, the eligibility criteria were met by 19 studies (Table 1). These were supplemented with one more study found through a reference search. Two studies used the same dataset [12,13], but both were included due to the different methods adopted for assessment of CA. However, 11 studies were included in the quantitative analysis comparing $ETCO_2$ levels in acute stroke and control groups.

3.2. Risk of bias in included studies

According to the results of the NOS, 12 out of the 20 studies scored 8 to 9 points indicating high methodological quality. Supplemental material Table III provides the risk of bias indicators of the included studies.

3.3. Main findings of included studies

Acute stroke patients recruited in five studies had intracerebral

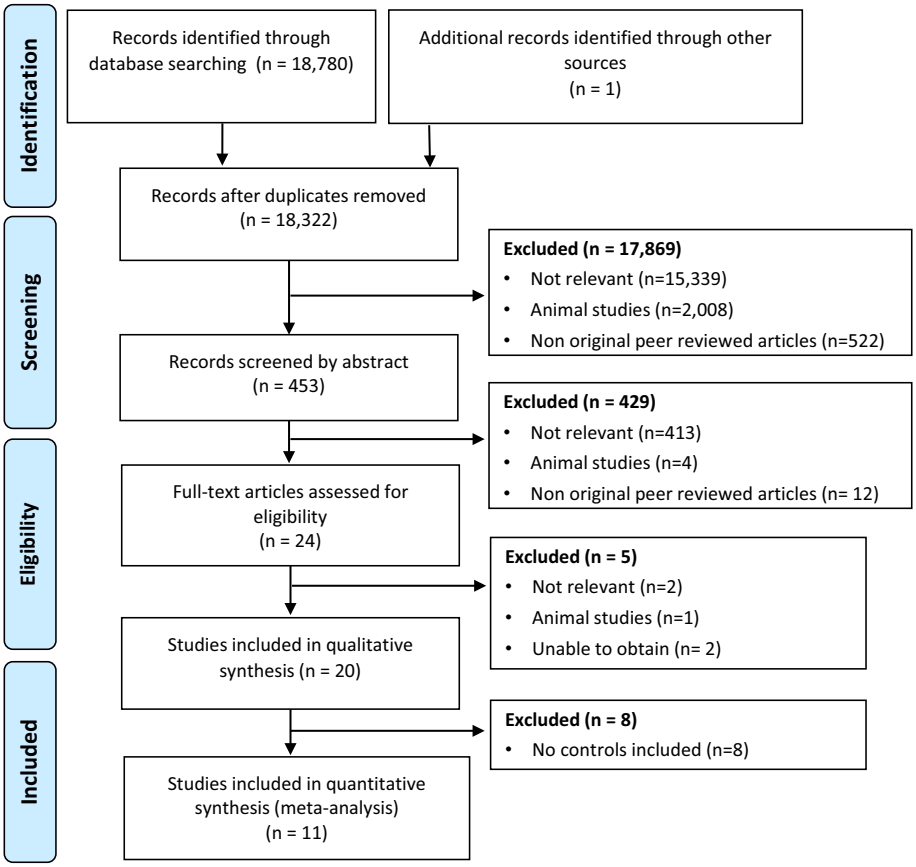

Fig. 1. Flowchart of article inclusion.

hemorrhage (ICH) and in fifteen studies had acute ischemic stroke (AIS). NIHSS varied between 7.4 ± 5.0 and 12 ± 7.0 in the ICH patients, and 3.5 ± 3.3 and 20 [IQR not informed] in the AIS patients, with one study not reporting stroke severity in ICH [14] and two studies in AIS [15,16]. The total number of participants was significantly higher in the stroke group (n = 660) than the control group (n = 384); most of the included participants being male (n = 426, 65%). Seven studies did not include controls [14,17–22]. CA assessment was performed in 18 studies and the method used to calculate was transfer function analysis (TFA) in 11 studies [12,13,15,18,19,22–27], and autoregulation index (ARI) in four studies [5,17,28–30]; with rate of regulation (RoR) [16], flow values [14] and cerebral perfusion pressure-oxygen reactivity index (COR) [21] being used in one study each. All studies, except those previously stated as lacking control data, included CO_2 (mmHg) data for acute stroke patients and controls. Main findings of the included studies are presented in Table 1. The lowest $EtCO_2$ values were 31.4 ± 3.8 mmHg within the AIS population [27] and the highest values 43.2 ± 5.4 mmHg were those derived in MCA AIS [21].

3.4. Meta-analysis of outcomes

All studies detailed carbon dioxide values ($ETCO_2$ or $PaCO_2$) for acute stroke patients, whereas two studies did not present $ETCO_2$ data from controls [12,13], and seven studies recruited no controls [14,17–22]. Therefore, only 11 studies were eligible for carbon dioxide meta-analysis. Pooled analysis showed statistically significant hypocapnia in AIS compared to healthy control subjects with high heterogeneity between studies (−1.52 mmHg [95% CI -2.66 to −0.38], p = .009; I^2 = 81%), as presented in Fig. 2. The meta-analysis also indicated significant decrease in CBFV bilaterally in acute stroke compared to healthy controls; pooled mean difference of $-8.72\ cm.s^{-1}$ [95% CI -12.04 to −5.39, p < .00001 (Fig. 3)] and $-6.98\ cm.s^{-1}$ [95% CI −8.83 to −5.13, p < .00001 (Fig. 4)], for affected and unaffected hemispheres, respectively. Due to different methods used to assess CA, only analysis of the differences in phase between acute stroke and controls could be performed. The meta-analysis of 5 studies indicated bilateral CA impairment in acute stroke, pooled significant mean difference of −24.76 degrees of phase [95% CI -35.09 to −14.44, p < .00001 (Fig. 5)] and −24.60 [95% CI -34.28 to −14.91, p < .00001 (Fig. 6)], for affected and unaffected hemispheres, respectively. ARI was assessed in five studies [5,17,28,29,31].

3.5. Meta-regression

Random-effects meta-regression was performed to assess the CO_2 levels on study outcomes (Table 2), and to assess the impact of potential moderator variables on $PaCO_2$ levels in the included studies. Of the covariates selected, data on sex, age and BP were available for 11 studies, whereas admission NIHS was described in 8 studies. Higher admissions NIHSS was significantly associated with hypocapnia (P = .01). Meta-regression showed no particular influence of any other moderator.

4. Discussion

This study demonstrates, for the first time, that acute stroke patients are significantly more likely than controls to be hypocapnic. Furthermore, both affected and unaffected hemispheres in acute stroke patients display convincingly lower CBFV than control subjects and impairment of CA, as evidenced by reduced TFA phase in comparison with control subjects. This review incorporates significant numbers of acute stroke patients (> 500), with detailed physiological measurement assessments, using highly comparable methodological approaches.

Table 1
Characteristics of included studies.

Study	Stroke type	Stroke severity (mean NIHSS)	Number patients (controls)	Sex M:F patients (controls)	Age patients (controls)	Time from onset	MAP, mmHg	CBFV ($cm.s^{-1}$)			Cerebral autoregulation	Conclusion summary	Carbon dioxide (mm Hg)	
								AH	UH	Controls	Assess. method		Stroke	Controls
AIS														
Castro et al., 2017a	AIS	18.2 ± 10.5	46 (NC)	25:21 (NC)	73.0 ± 12.0 (NC)	< 6h	97.0 ± 11.0 (NC)	51.0 ± 18.0	53.0 ± 16.0	NC	TFA	Impaired AH (lower PD, HT group only)	36.0 ± 7.0	NC
Castro et al., 2017b	AIS	11.9 ± 9.0	30 (NC)	16:14 (NC)	69.0 ± 13.0 (NC)	< 6h	81.0 ± 14.0 (NC)	42.0 ± 15.0	50.0 ± 18.0	NC	TFA	Lower PD and gain in poor outcome patients	37.0 ± 6.0	NC
Castro et al., 2018	AIS	14.9 ± 15.6	46 (NC)	19:27 (NC)	73 ± 12 (NC)	< 6h	98.0 ± 11.0 (NC)	40.0 ± 20.0	48.0 ± 17.0	NC	TFA	Higher gain in impaired renal function patients	36.0 ± 7.0	NC
Dohmen et al., 2007	malignant AIS	20 ± NS	8 (NC)	5:3 (NC)	55.0 ± 6.0 (NC)	24.0h ± 4.0 & 72.0h ± 4.0	135.7 ± 16.5 (NC)	NS	NS	NC	COR	Impaired in patients with malignant oedema	39.7 ± 2.1 (early) 40.3 ± 2.4 (late)[a]	NC
	benign AIS	16 ± NS	7 (NC)	5:2 (NC)	61.0 ± 8.0 (NC)		121.7 ± 13.8 (NC)	NS	NS	NC	COR	Preserved in patients without malignant oedema	40.0 ± 2.5 (early) 43.2 ± 5.4 (late)[a]	NC
Guo et al., 2014	AIS (LAA)	7.1 ± 4.7	15(20)	12:03 (16:4)	44.7 ± 13.1 (42.2 ± 13.7)	120-240h	LAA: 90.0 ± 17.0 SAO:101.5 ± 19.7 Control:89.5 ± 16.0	NS	NS	NS	TFA	Impaired AH (lower PD)	36.2 ± 2.6	36.4 ± 2.4
	AIS (SAO)	3.8 ± 2.8	26 (20)	21:05 (16:4)	54.1 ± 9.7 (42.2 ± 13.7)			NS	NS	NS	TFA	Impaired bilaterally (lower PD)	37.2 ± 2.9	36.4 ± 2.4
Guo et al., 2015	AIS	3.7 ± 1.9	46 (30)	30:16 (20:10)	54.3 ± 9.4 (53.7 ± 10.6)	< 48h	AIS: 100.4 ± 17.7 Controls: 89.9 ± 9.6	NS	NS	NS	TFA	Impaired bilaterally (lower PD)	37.2 ± 2.4	36.1 ± 2.8
Lam et al., 2018	AIS	4.8 ± 4.2	15 (16)	7:8 (8:8)	69.0 ± 7.5 (57.0 ± 16.0)	13.3 ± 6.9 h	AIS: 101.0 ± 17.0 Control: 89.5 ± 11.6	38.3 ± 14.4	43.4 ± 14.9	52.6 ± 13.6	ARI	No difference between groups	33.5 ± 2.7	38.9 ± 3.5
Llwyd et al., 2018	AIS	≤ 5	65 (NC)	39:26 (NC)	66.0 ± 12.0 (NC)	19h [IQR5-30]	100.1 ± 12.0 (NC)	41.0 ± 13.0	45.0 ± 14.0	NC	ARI	No differences between AH/UH	35.0 ± 3.0	NC
	AIS	6 - 25	56 (NC)	32:24 (NC)	64.0 ± 14.0 (NC)			43.0 ± 17.0	51.0 ± 18.0	NC	ARI	No differences between AH/UH	36.0 ± 3.0	NC
Panerai et al., 2016	AIS	NS	11 (9)	83:72 (7:2)	69.9 ± 39.9 (60.0 ± 24.4)	< 48h	AIS: 97.4 ± 21.4 Control: 96.9 ± 19.6	45.2 ± 8.9	42.3 ± 9.8	L: 50.9 ± 8.7 R: 49.5 ± 5.2	RoR	Impaired bilaterally	35.5 ± 3.1	39.6 ± 2.6[b]
Salinet et al., 2014	AIS	7.8 ± 4.8	15 (22)	12:03 (16:6)	62.4 ± 9.0 (62.2 ± 7.5)	36.6h ± 15.5	AIS: 91.9 ± 8.7 Control: 87.2 ± 11.0	45.4 ± 6.9	49.5 ± 10.1	L: 50.7 ± 5.6 R: 48.9 ± 4.9	ARI	Impaired CA and NVC initially but improved over time	35.1 ± 2.6	37.7 ± 3.2[b]
Salinet et al., 2015	AIS	3.5 ± 3.3	27 (27)	16:11 (15:12)	63.0 ± 11.7 (61.4 ± 6.0)	32.6h ± 14.0	AIS: 86.1 ± 20.1 Control: 91.0 ± 19.3	43.5 ± 19.0	41.1 ± 11.0	49.6 ± 10.5	ARI	Preserved CA	34.4 ± 3.4	38.9 ± 4.5[b]

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Table 1 (*continued*)

Study	Stroke type	Stroke severity (mean NIHSS)	Number patients (controls)	Sex M:F patients (controls)	Age patients (controls)	Time from onset	MAP, mmHg	CBFV (cm.s^{-1})			Cerebral autoregulation	Conclusion summary	Carbon dioxide (mm Hg)	
								AH	UH	Controls	Assess. method		Stroke	Controls
Salinet et al., 2018	AIS	14.9 ± 7.1	55 (32)	27:28 (10:22)	62.8 ± 12.0 (63.6 ± 10.4)	28.9h ± 12.0	AIS: 89.9 ± 20.1 Control: 93.1 ± 12.2	42.4 ± 10.0	50.4 ± 9.7	58.0 ± 9.2	ARI	Impaired with increasing severity	38.4 ± 1.3	38.9 ± 1.0
Takahashi et al., 2014	AIS (good outcome)	Median 18 [IQR NS]	NS	NS	61.8 ± NS (NC)	NS	109 ± NS (NC)	NC	NC	NC	NA	General anesthesia	35.2 ± NS	NC
	AIS (poor outcome)	Median 20 [IQR NS]	NS	NS	69.4 ± NS (NC)			NC	NC	NC	NA	resulted in decrease in BP and EtCO2. Only lower ETCO2 values were associated with unfavorable functional outcomes with unfavorable functional outcomes at 90 days.	34.1 ± NS	NC
Tutaj et al., 2014	AIS	5.3 ± 2.8	6 (14)	04:02 (7:7)	65.5 ± 9.2 (61.8 ± 9.7)	< 72h	AIS: 90.7 ± 5.5 Control: 84.6 ± 3.5	27.7 ± 5.9	26.9 ± 2.9	34.4 ± 4.7	TFA	Impaired UH (lower PD)	31.4 ± 3.8	32.1 ± 1.7
Wang et al., 2015	AIS	NS	8 (24)	07:01 (12:12)	49.3 ± 4.3 (48.3 ± 7.2)	NS	NS	NC	NC	NC	TFA	Impaired bilaterally (lower PD bilaterally and gain UH)	35.5 ± 2.6	35.5 ± 2.1
ICH														
Ma et al., 2016	ICH	7.4 ± 5.0	43 (30)	30:13 (21:9)	53.7 ± 10.0 (52.3 ± 8.1)	< 48h & 96-120h	ICH: 122.5 ± 15.1[b]/117.2 ± 14.1[b] Control: 92.3 ± 11.6	D1-2: 49.6 ± 19.1 D4-6: 56.0 ± 17.2	D1-2: 52.3 ± 20.6 D4-6: 58.4 ± 16.7	62.9 ± 13.0	TFA	Impaired bilaterally (lower PD)	D1-2: 34.3 ± 3.7 D4-6: 34.9 ± 2.8	35.1 ± 2.5
Ma et al., 2017	ICH	7.6 ± 5.1	53 (30)	40:13 (21:9)	54.3 ± 11.1 (52.3 ± 8.1)	< 144h	ICH: 110.6 ± 15.2[b] Control: 92.3 ± 11.6	53.6 ± 17.1	57.2 ± 14.5	62.9 ± 13.0	TFA	Impaired bilaterally (lower PD)	34.7 ± 3.3	35.1 ± 2.5
Oeinck et al., 2013	ICH	12.0 ± 7.0	26 (55)	21:05 (44:11)	65.0 ± 11.0 (64.0 ± 8.0)	< 24h, 72h & 120h	D1: 96.1 (NS) D3: 101.7 (NS) D5: 100.0 (NS)	D1: 43.6 (SE =3.4) D3: 55.8 (SE =3.6) D5: 53.6 (SE =3.6)	D1: 47.7 (SE=3.5) D3: 56.6 (SE=3.7) D5: 47.7 (SE=3.5)	NS	TFA	Preserved PD but impaired gain bilaterally	D1: 34.9 (SE=0.9) D3: 34.3 (SE=0.9) D5:35.1 (SE=0.9)	NS
Reinhard et al., 2010	ICH	12.0 ± 7.0	26 (55)	21:05 (44:11)	65.0 ± 11.0 (64.0 ± 8.0)	< 24h, 72h & 120h	D1: 90.9 (SE =4.6) D3: 85.5 (SE = 4.5) D5: 84.4 (SE = 4.5)	D1: 43.6 (SE = 3.4) D3: 55.8 (SE = 3.6) D5: 53.6 (SE = 3.6)	D1: 47.7 (SE 3.5) D3: 56.6 (SE 3.7) D5: 47.7 (SE 3.5)	NS	TFA (Mx)	Preserved with secondary decline in AH	D1: 34.9 (SE=0.9) D3: 34.3 (SE=0.9) D5:35.1 (SE=0.9)	NS

(*continued on next page*)

Table 1 (*continued*)

Study	Stroke type	Stroke severity (mean NIHSS)	Number patients (controls)	Sex M:F patients (controls)	Age patients (controls)	Time from onset	MAP, mmHg	CBFV ($cm.s^{-1}$)			Cerebral autoregulation		Conclusion summary	Carbon dioxide (mm Hg)	
								AH	UH	Controls	Assess. method			Stroke	Controls
Ye and Su, 2013	ICH	NS	30 (NC)	23:07 (NC)	58.0 ± 13.0 (NC)	< 120h	115 ± 16 (NC)	52.0 ± 15.0	49.0 ± 11.0	NC	PI		Impaired PI	40.11 ± 5.5[a]	NC

LAA, large-artery atherosclerosis; AH, affected hemisphere; AIS, acute ischemic stroke, ARI, autoregulatory index; CA, cerebral autoregulation; CBFV, cerebral blood flow velocity; COR, cerebral perfusion pressure-oxygen reactivity index; D, day; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; IQR, interquartile; MCA, middle cerebral artery; Mx, mean flow index; NA, not applicable; NS, not stated; NC, no controls included in the study; NVC, neurovascular coupling; PD, phase difference; PI, pulsatility index; SE, standard error; SAO, Small-artery occlusion, RoR, rate of return; TFA, transfer function analysis; UH, unaffected hemisphere.

[a] $PaCO_2$ (not $ETCO_2$ like others).

[b] Statistical difference between controls and stroke.

Importantly, the volume of data on CO_2 levels in acute stroke provides an evolution on previous reviews [32], which states "interpretation of measurements can be severely confounded in situations in which significant changes in CO_2 go undetected." Despite this study providing further confirmatory evidence of the bilateral impairment of CA, the processes governing change from impairment to improvement remain unclear. Nevertheless, impairment of CA has recently been correlated with stroke severity and functional outcome [29]. The information afforded by continuous monitoring of $PaCO_2$ (capnography), blood pressure (beat-to-beat) and CBFV (TCD), as is often the case in autoregulatory studies, provides a wealth of data on potential physiological and pathological mechanisms during acute stroke.

$PaCO_2$ change has a strong influence on cardio- and cerebro-vascular variables. Key studies in stroke populations, designed to assess impairment of dynamic CA in acute stroke, have often been hampered by the inability to adjust for perceived lower levels of $PaCO_2$ post stroke [5,33]. In non-neurological disease states two important studies exist to provide some perspective on cardio-respiratory disease and haemodynamics [34] and chronic kidney disease (associated with increased cardiorespiratory morbidity) [22]. These two studies both demonstrated impaired dynamic cerebral autoregulation and provide evidence to support an underlying mechanism for the increased stroke risk we see in these two populations. To date, our understanding of the relationship between $PaCO_2$ and CBF is largely informed by healthy volunteer studies using protocols designed to assess blood flow across the physiological range of $PaCO_2$ [4,35,36,38]. Despite such studies offering a potential opportunity to "correct" for $PaCO_2$ variation post-stroke, there has been a lack of confirmatory evidence to support the hypothesis that acute stroke patients are indeed hypocapnic. Furthermore, there are no comparative studies to date assessing both ICH and AIS patients in this context.

Hypocapnia is considered a common component of several acute disease states including cardiopulmonary diseases, such as early asthma and pulmonary oedema [3]. Furthermore, assessment of acid-base disturbance has long formed part of the acute work-up of a deteriorating patient. Our understanding of the clinical profile of hypocapnia in the critically ill patient is limited [37]. The potential benefits of hypocapnia in critical illness include prevention of brainstem herniation and prevention of hypertensive crises in neonates [37]. However, potential risks are associated primarily with the impact on respiratory physiology with hypocapnia often manifesting in acute respiratory distress syndrome [37]. This is associated with increased airway resistance and worsened ventilation/perfusion matching [37]. Interestingly, hyperventilation and hypocapnia have been identified as independent determinants of long-term pulmonary dysfunction in patients with underlying lung disease [37]. By understanding the relationship between hypocapnia and acute stroke, there exists direction of research to identify a biomarker of evolving lung pathology post-stroke (pneumonia for example) or indeed an exacerbation of existing chronic lung disease. However, aside from head injury and certain 'brain at risk' states like epilepsy and cardiac arrest, no guidelines exist encouraging assessment of hypocapnia specifically in acute stroke. The neurologic effects of hypocapnia include lowering of intracranial pressure (by hypocapnic alkalosis decreasing CBF by vasoconstriction) and deleterious effects including risk of reperfusion injury by cerebral hyperemia, post normalisation, post hypocapnia [3]. However, no studies to date have clarified whether hypocapnia is a neuroprotective mechanism or a consequence of disease pathology. Studies are ongoing to assess the potential for manipulation of CO_2 levels via hyperventilation in acute ICH [8] with a hope that improved autoregulation associated with lower levels of $PaCO_2$ may potentiate improved outcome by expanding the plateau region of the autoregulatory curve and keeping CBF constant over a wider range of perfusion pressures as seen in the neurologically vulnerable acute ICH patient cohort.

This review once again highlights the complex interplay that governs $PaCO_2$ levels, autoregulatory impairment and acute stroke

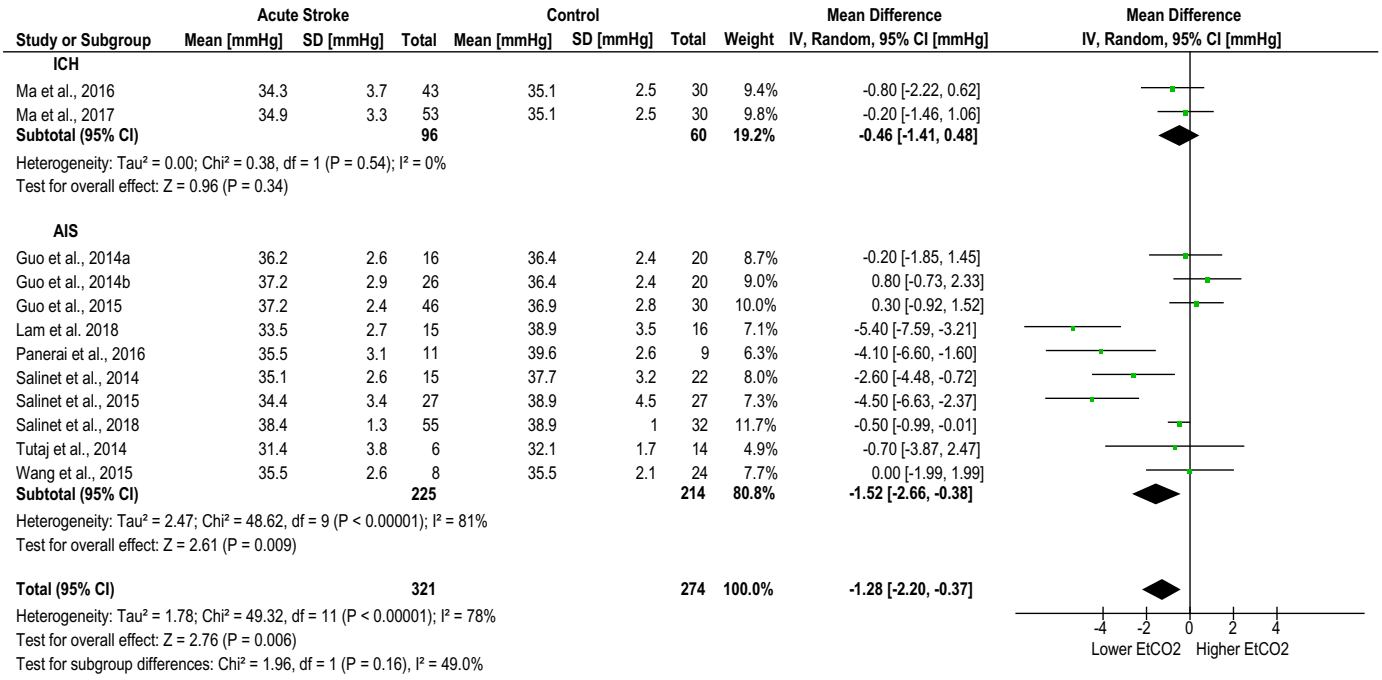

Fig. 2. Forest plot with random effects for differences in $EtCO_2$ levels between acute stroke and healthy controls.

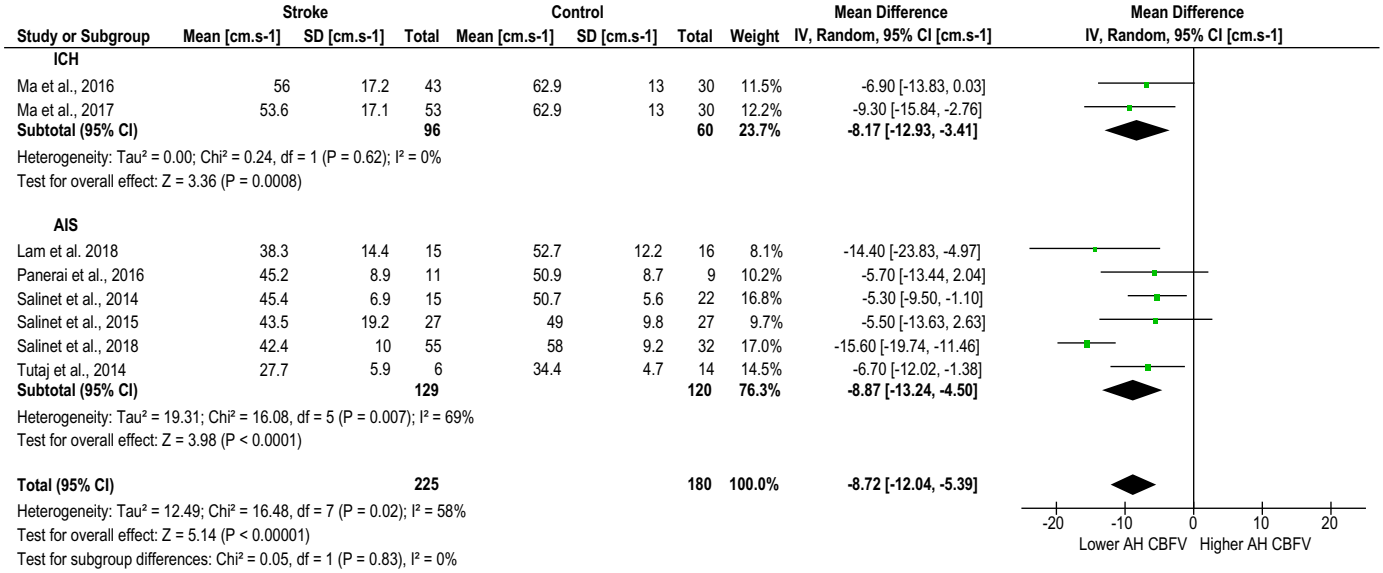

Fig. 3. Forest plot with random effects for differences in the affected hemisphere CBFV between acute stroke and healthy controls.

physiological perturbations [33]. There are several limitations within this review. Firstly, review protocol was not registered in any systematic review database. However, the authors conducted careful examination of databases, including PROSPERO and Cochrane, to ensure no similar reviews were being undertaken. Secondly, it was included in the meta-analysis more AIS studies than ICH. However, this represents the incidence of stroke as AIS occurs more frequently than ICH. Lastly, the review is limited to data reported in the selected articles and the authors did not perform individual patient data meta-analyses. However, the methodological quality of included studies was carefully assessed using pre-specified objective criteria and therefore the findings should be considered robust.

Hypocapnia generated by hyperventilation is associated with improvement in cerebral autoregulation across both healthy and diseased states [4,39,40], and provides clinically preferential benefits on circumstances associated with raised ICP [41,42]. However, with this study demonstrating that CA remains impaired despite the existence of a mild but consistently apparent hypocapnic state, is this considered a physiological response designed to precipitate neuroprotection? If the baseline hypocapnic state were accentuated post stroke, would CA improve or would we see a u-shaped curve worsening of CA as hypocapnia accentuated. Furthermore, to what extent does vasoconstriction associated with hypocapnia become a concern in acute stroke? This remains unclear and future studies are required to answer these specific questions associated with reasoning for hypocapnia existing post stroke.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

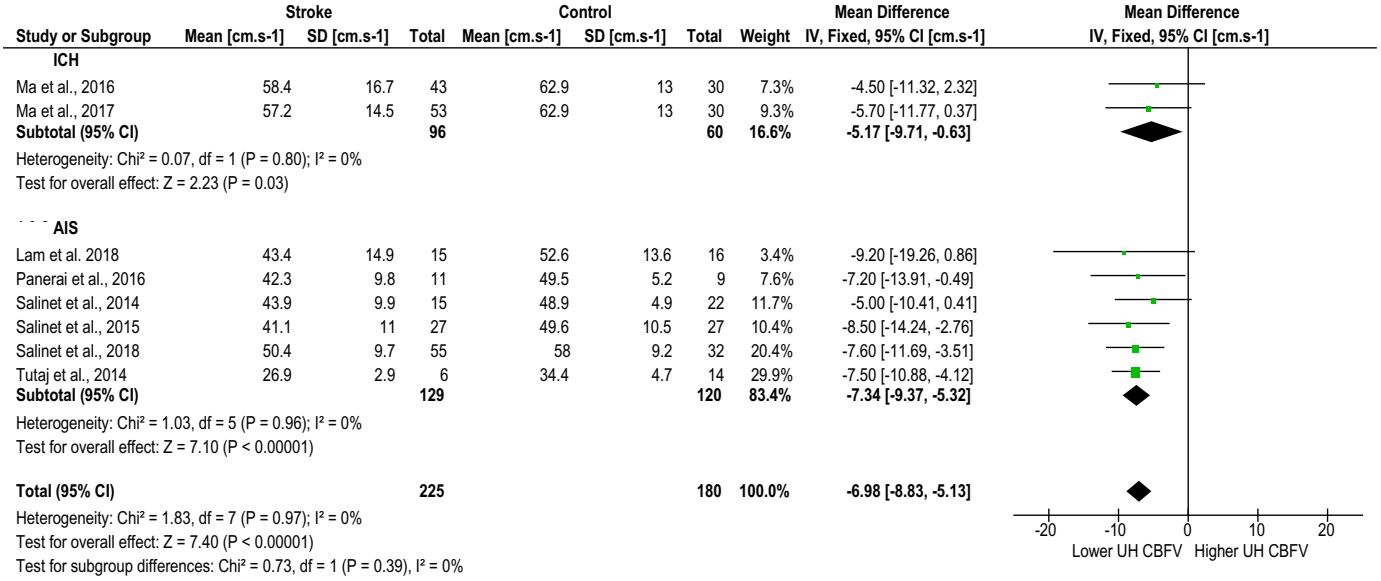

Fig. 4. Forest plot with fixed effects for differences in the unaffected hemisphere CBFV between acute stroke and healthy controls.

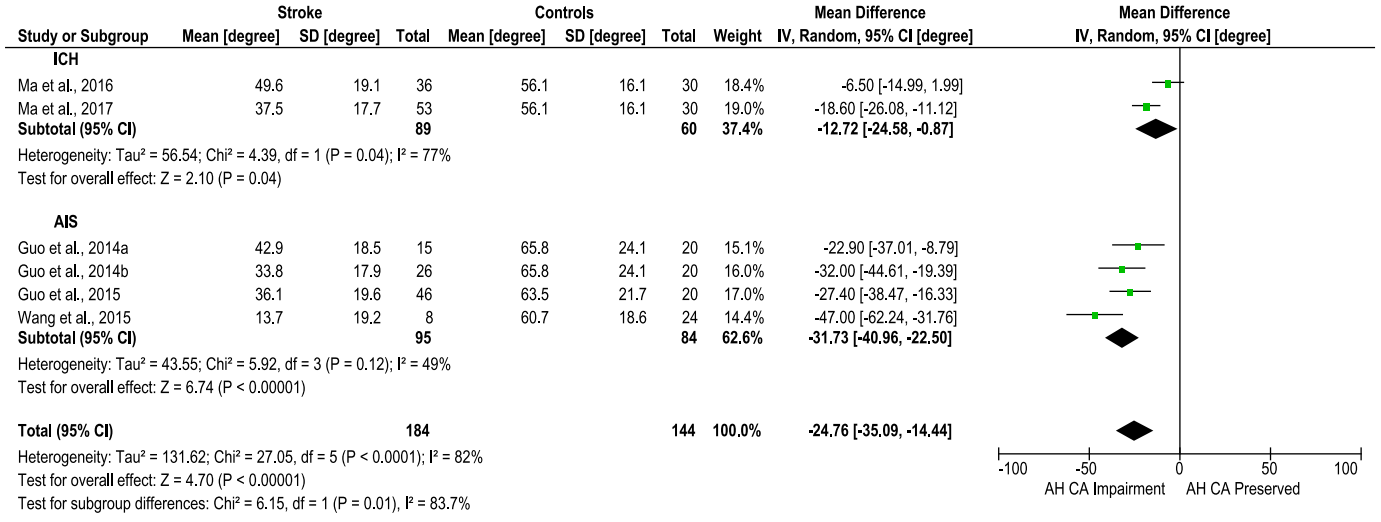

Fig. 5. Forest plot with fixed effects for differences in the affected hemisphere CA (phase difference) between acute stroke and healthy controls.

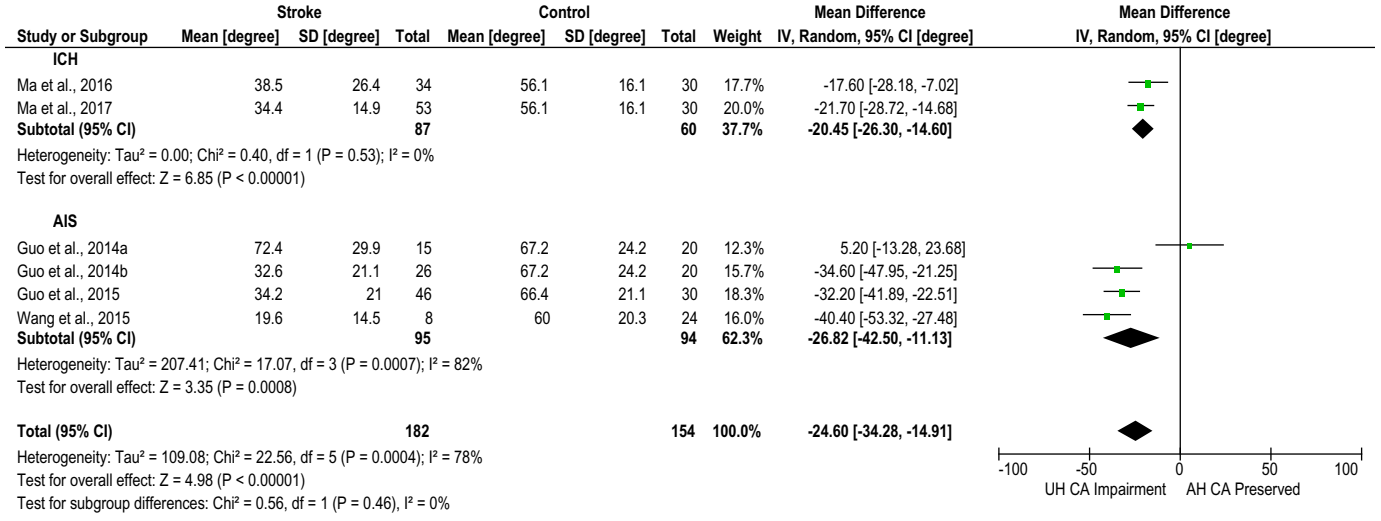

Fig. 6. Forest plot with fixed effects for differences in the unaffected hemisphere CA (phase difference) between acute stroke and healthy controls.

Table 2
Summary of meta-regression of carbon dioxide levels and covariates.

Covariate	B	Exp (B) 95% CI	Sig. (p)
Mean Age, y	0.0174	−0.0429, 0.0772	0.225
Male/gender	0.0602	−0.1234, 0.2506	0.412
Mean ABP, mmHg	0.0520	−0.1076, 0.2079	0.622
Admission NIHSS	0.5379	0.2764, 0.8211	0.010
AH CBFV, $cm.s^{-1}$	0.0139	−0.0501, 0.0986	0.544
UH CBFV, $cm.s^{-1}$	0.0580	−0.0836, 0.1788	0.570
AH CA (TFA)	0.0147	−0.0432, 0.0727	0.252
UH CA (TFA)	0.0324	−0.0772, 0.1402	0.405

ABP, arterial blood pressure; NIHSS, National Institutes of Health Stroke Scale; AH, affected hemisphere; UH, unaffected hemisphere; CBFV, cerebral blood flow; CA, cerebral autoregulation; TFA, transfer function analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.04.038.

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