

## Original Paper

# Cerebral Haemodynamics following Acute Ischaemic Stroke: Effects of Stroke Severity and Stroke Subtype

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## Keywords

Blood flow velocity · Cerebral autoregulation · Acute stroke · Stroke subtype · Stroke severity

## Abstract

**Background:** Acute ischaemic stroke (AIS) patients often show impaired cerebral autoregulation (CA). We tested the hypothesis that CA impairment and other alterations in cerebral haemodynamics are associated with stroke subtype and severity. **Methods:** AIS patients ( $n = 143$ ) were amalgamated from similar studies. Data from baseline (<48 h stroke onset) physiological recordings (beat-to-beat blood pressure [BP], cerebral blood flow velocity (CBFV) from bilateral insonation of the middle cerebral arteries) were calculated for mean values and autoregulation index (ARI). Differences were assessed between stroke subtype (Oxfordshire Community Stroke Project [OCSP] classification) and severity (National Institutes of Health Stroke Scale [NIHSS] score <5 and 5–25). Correlation coefficients assessed associations between NIHSS and physiological measurements. **Results:** Thirty-two percent of AIS patients had impaired CA (ARI <4) in affected hemisphere (AH) that was similar between stroke subtypes and severity. CBFV in AH was comparable between stroke subtype and severity. In unaffected hemisphere (UH), differences existed in mean CBFV between lacunar and total anterior circulation OSCP subtypes (42 vs. 56  $\text{cm} \cdot \text{s}^{-1}$ ,  $p < 0.01$ ), and mild and moderate-to-severe stroke severity (45 vs. 51  $\text{cm} \cdot \text{s}^{-1}$ ,  $p = 0.04$ ). NIHSS was associated with peripheral (diastolic and mean

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arterial BP) and cerebral haemodynamic parameters (CBFV and ARI) in the UH. **Conclusions:** AIS patients with different OCSF subtypes and severity have homogeneity in CA capability. Cerebral haemodynamic measurements in the UH were distinguishable between stroke subtype and severity, including the association between deteriorating ARI in UH with stroke severity. More studies are needed to determine their clinical significance and to understand the determinants of CA impairment in AIS patients.

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## Introduction

Transcranial Doppler ultrasound has been widely used to evaluate cerebral haemodynamics in acute ischaemic stroke (AIS) patients, as it offers a non-invasive and real-time monitoring of cerebral blood flow velocity (CBFV). In particular, the assessment of cerebral autoregulation (CA), which reflects changes in CBF in relation to changes in blood pressure (BP), has provided further understanding of cerebral haemodynamic control [1]. Whilst previous studies have reported impairment of CA following acute stroke [2, 3], there are limited data on the effects of stroke subtype and severity. Cortical stroke appears to be associated with reduced CA, more often in the affected hemisphere (AH), whereas subcortical stroke may be associated with bilateral impairment [4, 5]. Stroke severity may also be relevant, with moderate-to-severe stroke exhibiting greater CA impairment compared to minor stroke [6–9]. However, small sample size, and methodological heterogeneity in both data collection and analysis limit informed comparison between studies [10].

The Cerebral Haemodynamics in Ageing and Stroke Medicine (CHiASM) at the University of Leicester has a longstanding interest in studies of cerebral haemodynamic control mechanisms in the acute and recovery phases of AIS [7, 11–14]. Together with collaborators from the Hospital das Clinicas (São Paulo, Brazil), trained in cerebral haemodynamic assessment in Leicester, we have developed a large two-centre prospective database of AIS patients, utilising similar techniques in data acquisition and analysis that allow the interpretation of the effects of stroke severity and subtype on cerebral haemodynamic responses. We tested the hypothesis that stroke subtype or stroke severity significantly affects CA and consequently CBF precipitated by fluctuations in BP.

## Methods

All investigators were trained at the same laboratory (University of Leicester, UK), and acquired physiological data to a standard data collection and analysis protocol. AIS patients admitted to the University Hospitals of Leicester NHS Trust (Leicester, UK), since 2007, or to the Hospital das Clinicas (São Paulo, Brazil), since 2015, and eligible for inclusion into ongoing studies of cerebral haemodynamics in AIS, were recruited and provided informed consent in compliance with local ethics committee approvals. All studies had common inclusion criteria: patients with clinical diagnosis of AIS, aged  $\geq 18$  years, able to participate in study measurements, and informed consent; a common exclusion criterion was co-morbidity with life expectancy less than 3 months. In addition, patients were excluded from the database if: (a) missing key information (age, sex, and classification of stroke subtype according to Oxfordshire Community Stroke Project [OCSF] classification), (b) poor data quality, (c) duplicates arising from overlapping studies, (d) AIS classified as posterior circulation stroke, (e) physiological measurements performed after 48 h from stroke onset.

The same protocol was used for all studies. Briefly, beat-to-beat BP was recorded continuously using the Finapres or Finometer devices (FMS, Finapres Measurement Systems, Arnhem, Netherlands). Heart rate (HR) was recorded using a 3-lead electrocardiogram, and end-tidal CO<sub>2</sub> (etCO<sub>2</sub>) was measured via nasal prongs (Salter Labs) by an infrared capnograph (Capnocheck Plus and Transmai MX-200 in Leicester and São Paulo, respectively). Bilateral insonation of the middle cerebral arteries was performed using transcranial Doppler (Viasys Companion III; Viasys Healthcare and Doppler box, DWL for Leicester and São Paulo, respectively) with a 2-MHz probe, secured in place using a head-frame. Subjects were in a supine position. Systolic and diastolic BP was measured by brachial sphygmomanometry followed by 15-min stabilisation and 5-min baseline recording. When more than one baseline recording was available, the first acceptable recording was used for further analysis. Stroke subtype was defined by the OCSF classification; stroke severity was assessed by the NIHSS on hospital admission and at the time of cerebral haemodynamic assessment, with further categorisation by mild (NIHSS ≤5) [15] and moderate-to-severe stroke (NIHSS 6–25) [16].

#### *Data Analysis*

This has been described in detail previously [17]. In brief, data were simultaneously recorded onto a data acquisition system (PHYSIDAS, Department of Medical Physics, University Hospitals of Leicester) for subsequent off-line analysis. BP was calibrated at the start of each recording using systolic and diastolic values from brachial sphygmomanometry. The R–R interval was automatically marked from the electrocardiogram and mean BP and CBFV values were calculated for each cardiac cycle. If the etCO<sub>2</sub> recording was not consistent due to periods of breathing through the mouth, the highest etCO<sub>2</sub> value was used.

Autoregulation index (ARI), which represents dynamic CA, was extracted by using the best least-squares fit between the CBFV step response and one of the 10 model ARI curves proposed by Tiecks et al. [18]. Values of ARI were only accepted for further analyses if strict conditions were met regarding the significance of the coherence between mean arterial BP CBFV and the normalised mean square error of fit to Tiecks model [19].

#### *Statistical Analysis*

Mean values of each variable were calculated from the entire baseline recording. Tests for normality were performed using the Shapiro-Wilk normality test. Data are presented as median and interquartile range (25th–75th percentile) and mean (SD) unless stated otherwise. Parameter values were considered outliers and excluded from further analysis if they were ±3 SD from the mean for all stroke patients. Differences between values derived from the AH or unaffected hemisphere (UH) were assessed with paired Student's *t* test or the Wilcoxon test. Differences in variables between OCSF subtypes were assessed using a  $\chi^2$  test, Fisher's exact test, ANOVA or Kruskal-Wallis test, followed by Tukey's or Dunn's multiple comparison test. Differences in variables between categorised NIHSS were assessed with Fisher's exact test, unpaired Student's *t* test or Mann-Whitney test. Associations between variables were tested using linear regression correlation coefficient or Spearman's rank test as appropriate, where NIHSS was considered as a continuous variable. A *p* value of <0.05 was defined as statistical significance.

## **Results**

#### *Study Population*

Data for 143 AIS patients (105 Leicester; 38 São Paulo) of mean age 65 years (SD 13; 37% female) with good quality baseline recordings were included. Key baseline characteristics are

**Table 1.** Key baseline patient characteristics

| Variable                        | n     |                     |
|---------------------------------|-------|---------------------|
| Total patients                  | 143   |                     |
| Demographics                    |       |                     |
| Female                          | 53    | (37)                |
| Age, years                      | 143   | 65 [13]             |
| Patient history                 |       |                     |
| Smoker                          | 21    | (19)                |
| Ex-smoker                       | 37    | (33)                |
| Ischaemic heart disease         | 31    | (25)                |
| Cerebrovascular disease         | 22    | (18)                |
| Diabetes mellitus               | 18    | (14)                |
| Hypertension                    | 62    | (50)                |
| Antihypertensive therapy        | 57    | (56)                |
| Statin therapy                  | 29    | (29)                |
| Aspirin/antiplatelet/warfarin   | 23    | (23)                |
| Ipsilateral ICA stenosis >50%   | 20    | (24)                |
| Contralateral ICA stenosis >50% | 4     | (5)                 |
| AIS features                    |       |                     |
| LACS                            | 53    | (37)                |
| PACS                            | 66    | (46)                |
| TACS                            | 24    | (17)                |
| Onset to recording, h           | 117   | 19 (5–30)           |
| Time of recording, 24 h         | 142   | 13:00 (11:11–15:30) |
| Thrombolysed                    | 40    | (49)                |
| Ipsilateral side, R/L           | 70/73 | (49/51)             |
| Admission NIHSS                 | 66    | 7 (4–12)            |
| Assessment NIHSS                | 122   | 5 (3–10)            |

Data are presented as n (% of available data), mean [standard deviation] or median (interquartile range, 25–75th percentile), as appropriate. n, number of participants; ICA, internal carotid artery; AIS, acute ischaemic stroke; R, right; L, left; NIHSS, National Institutes of Health Stroke Scale; LACS, lacunar stroke syndrome; PACS, partial anterior circulation stroke syndrome; TACS, total anterior circulation stroke syndrome.

described in Table 1. Of these, 115 patients had bilateral middle cerebral artery recordings; 9 had unilateral recordings only of the AH and 19 only of the UH. Assessments of cerebral haemodynamic parameters were undertaken a median of 19 h (IQR 5–30) after stroke onset, with 49% of patients treated with intravenous thrombolysis.

#### *Influence of Stroke Subtype*

Patient characteristics and peripheral and cerebral haemodynamic data are described in Table 2 by each stroke subtype; lacunar (LACS, n = 53), partial (PACS, n = 66) and total anterior circulation infarcts (TACS, n = 24). TACS patients were more likely to have a higher NIHSS and lower diastolic BP values at the time of haemodynamic assessment. With respect to differences in cerebral haemodynamic parameters between AH and UH, systolic, mean and diastolic CBFV were significantly higher in the UH in the TACS patients only. Regarding the comparison between stroke subtypes for AH and UH, only the UH had significant differences for systolic, mean and diastolic CBFV in the LACS compared to TACS patients, and additionally compared to PACS patients for diastolic CBFV alone. A poor goodness of fit to Tieck's model of CA was

**Table 2.** Patient characteristics and peripheral and cerebral haemodynamic parameters by stroke subtype

| Variable                               | LACS            |                        | PACS            |                      | TACS |               | p value |
|--|-----------------|------------------------|-----------------|----------------------|------|---------------|---------|
|  | n               |                        | n               |                      | n    |               |         |
| Demographics                           | 53              |                        | 66              |                      | 24   |               |         |
| Female                                 | 20              | (38)                   | 22              | (33)                 | 11   | (46)          | 0.55    |
| Age, years                             | 53              | 67 [12]                | 66              | 65 [14]              | 24   | 60 [15]       | 0.13    |
| AIS Features                           |                 |                        |                 |                      |      |               |         |
| Assessment NIHSS                       | 42              | 3 (1–4) <sup>†,‡</sup> | 57              | 5 (3–9) <sup>#</sup> | 23   | 15 (10–18)    | <0.001  |
| NIHSS <5                               | 33              | (79)                   | 29              | (51)                 | 3    | (13)          | <0.001  |
| NIHSS 6–25                             | 9               | (21)                   | 28              | (49)                 | 19   | (83)          | <0.001  |
| NIHSS >25                              | 0               |                        | 0               |                      | 1    | (4)           | 0.19    |
| Thrombolysed                           | 5               | (23)                   | 24              | (62)                 | 11   | (52)          | 0.01    |
| Onset to recording, h                  | 41              | 22 (14–36)             | 53              | 15 (3–30)            | 23   | 16 (6–28)     | 0.12    |
| Peripheral haemodynamic parameters     |                 |                        |                 |                      |      |               |         |
| MABP, mm Hg                            | 53              | 102 [16]               | 66              | 99 [13]              | 24   | 94 [11]       | 0.08    |
| Systolic BP, mm Hg                     | 53              | 149 [23]               | 66              | 144 [23]             | 24   | 142 [16]      | 0.36    |
| Diastolic BP, mm Hg                    | 52 <sup>§</sup> | 81 [14] <sup>#</sup>   | 66              | 77 [12]              | 24   | 72 [12]       | 0.03    |
| HR, beats/min                          | 52 <sup>§</sup> | 71 [10]                | 66              | 71 [13]              | 24   | 75 [14]       | 0.24    |
| etCO <sub>2</sub> , mm Hg              | 44              | 36 [3]                 | 49              | 36 [3]               | 15   | 36 [3]        | 0.93    |
| Cerebral haemodynamic parameters       |                 |                        |                 |                      |      |               |         |
| Mean CBFV, cm•s <sup>-1</sup> – A      | 47              | 40 [12]                | 56 <sup>§</sup> | 43 [16]              | 20   | 44 [15]*      | 0.48    |
| Mean CBFV, cm•s <sup>-1</sup> – U      | 50              | 42 [13] <sup>#</sup>   | 63              | 48 [16]              | 21   | 56 [19]       | <0.01   |
| Systolic CBFV, cm•s <sup>-1</sup> – A  | 47              | 64 [16]                | 56 <sup>§</sup> | 66 [24]              | 20   | 67 [24]*      | 0.77    |
| Systolic CBFV, cm•s <sup>-1</sup> – U  | 50              | 67 [18] <sup>#</sup>   | 63              | 75 [22]              | 21   | 86 [25]       | <0.01   |
| Diastolic CBFV, cm•s <sup>-1</sup> – A | 47              | 25 [10]                | 56 <sup>§</sup> | 28 [11]              | 20   | 29 [11]*      | 0.29    |
| Diastolic CBFV, cm•s <sup>-1</sup> – U | 50              | 26 [10] <sup>†,‡</sup> | 63              | 31 [12]              | 21   | 36 [13]       | <0.01   |
| ARI, arbitrary units – A               | 46              | 4.6 (3.7–6.0)          | 51              | 4.6 (3.6–6.2)        | 18   | 4.2 (3.6–5.4) | 0.82    |
| ARI, arbitrary units – U               | 48              | 4.4 (3.7–6.0)          | 56              | 4.8 (4.1–6.1)        | 17   | 4.1 (3.4–5.3) | 0.20    |
| ARI <4 – A                             | 15              | (33)                   | 17              | (33)                 | 5    | (28)          | 0.91    |
| ARI <4 – U                             | 13              | (27)                   | 13              | (23)                 | 8    | (47)          | 0.16    |

Data are presented as n (% of available data), mean [standard deviation] or median (interquartile range, 25th–75th percentile), as appropriate. p value, ANOVA or Kruskal-Wallis test between OCSF subtypes, followed by Tukey's or Dunn's multiple comparison test. n, number of participants; AIS, acute ischaemic stroke; NIHSS, National Institutes of Health Stroke Scale; MABP, mean arterial blood pressure; HR, heart rate; etCO<sub>2</sub>, end tidal CO<sub>2</sub>; CBFV, cerebral blood flow velocity; ARI, autoregulation index; A, affected hemisphere; U, unaffected hemisphere; LACS, lacunar stroke syndrome; PACS, partial anterior circulation stroke syndrome; TACS, total anterior circulation stroke syndrome. \* p < 0.05 vs. unaffected side. † p < 0.05 vs. PACS. # p < 0.05 vs. TACS. § Outlier removed from dataset.

found in 9 recordings from the AH and 13 from the UH. These values were not included in further ARI analysis, giving a total of 115 and 121 sets of data, respectively, 99 of these bilateral. No differences in ARI between the AH and UH or between the stroke subtypes were observed, including the number that had ARI <4 that could be suggestive of impaired CA (Table 2) [20].

### *Influence of Stroke Severity*

AIS patients were categorised into mild (n = 65) and moderate-to-severe (n = 56) stroke severity. Patient groups were of similar age and sex, with a significantly greater proportion of TACS and patients thrombolysed in the moderate-to-severe stroke group (Table 3). At the time of haemodynamic assessment, mild compared to moderate-to-severe stroke patients were more likely to have lower HR, and mean and diastolic CBFV in the UH; with haemodynamic assessment occurring later from stroke onset. With respect to differences in cerebral haemodynamic parameters between AH and UH, systolic and diastolic CBFV in the UH was higher in the moderate-to-severe stroke population. There were no differences observed in

**Table 3.** Patient characteristics and peripheral and cerebral haemodynamic parameters by mild and moderate-to-severe stroke severity

| Variable                               | Mild stroke<br>(NIHSS ≤5) |                         | Moderate-to-severe stroke<br>(NIHSS 6–25) |               | <i>p</i> value |
|--|---------------------------|-------------------------|---|---------------|----------------|
|  | <i>n</i>                  |                         | <i>n</i>                                  |               |                |
| Demographics                           | 65                        |                         | 56  |               |                |
| Female                                 | 26                        | (40)                    | 24  | (43)          | 0.85           |
| Age, years                             | 65                        | 66 [12]                 | 56  | 64 [14]       | 0.45           |
| AIS features                           |                           |                         |   |               |                |
| LACS                                   | 33                        | (51) <sup>†</sup>       | 9   | (16)          | <0.001         |
| PACS                                   | 29                        | (45)                    | 28  | (50)          | 0.59           |
| TACS                                   | 3                         | (5) <sup>†</sup>        | 19  | (34)          | <0.001         |
| Thrombolysed                           | 11                        | (33) <sup>†</sup>       | 27  | (60)          | 0.02           |
| Onset to recording, h                  | 61                        | 21 (11–31) <sup>†</sup> | 53  | 10 (3–27)     | 0.03           |
| Peripheral haemodynamic parameters     |                           |                         |   |               |                |
| MABP, mm Hg                            | 65                        | 100 [16]                | 56  | 98 [13]       | 0.52           |
| Systolic BP, mm Hg                     | 65                        | 145 [23]                | 56  | 143 [22]      | 0.69           |
| Diastolic BP, mm Hg                    | 64 <sup>§</sup>           | 79 [13]                 | 56  | 76 [13]       | 0.21           |
| HR, beats/min                          | 65                        | 69 [12] <sup>†</sup>    | 55 <sup>§</sup>                           | 74 [11]       | 0.03           |
| etCO <sub>2</sub> , mm Hg              | 52                        | 35 [3]                  | 35  | 36 [3]        | 0.38           |
| Cerebral haemodynamic parameters       |                           |                         |   |               |                |
| Mean CBFV, cm•s <sup>-1</sup> – A      | 58 <sup>§</sup>           | 41 [13]                 | 46  | 43 [17]       | 0.40           |
| Mean CBFV, cm•s <sup>-1</sup> – U      | 59                        | 45 [14] <sup>†</sup>    | 54  | 51 [18]       | 0.04           |
| Systolic CBFV, cm•s <sup>-1</sup> – A  | 58 <sup>§</sup>           | 64 [19]                 | 56  | 67 [25]*      | 0.43           |
| Systolic CBFV, cm•s <sup>-1</sup> – U  | 59                        | 71 [19]                 | 53  | 79 [25]       | 0.06           |
| Diastolic CBFV, cm•s <sup>-1</sup> – A | 58 <sup>§</sup>           | 26 [10]                 | 46  | 28 [12]*      | 0.41           |
| Diastolic CBFV, cm•s <sup>-1</sup> – U | 59                        | 28 [10] <sup>†</sup>    | 53  | 33 [13]       | 0.02           |
| ARI, arbitrary units – A               | 53                        | 5.0 (3.8–6.3)           | 43  | 4.3 (3.6–5.9) | 0.27           |
| ARI, arbitrary units – U               | 54                        | 5.1 (4.1–6.3)           | 46  | 4.4 (3.9–5.2) | 0.06           |
| ARI <4 – A                             | 15                        | (28)                    | 14  | (33)          | 0.66           |
| ARI <4 – U                             | 12                        | (22)                    | 13  | (28)          | 0.50           |

Data are presented as *n* (% of available data), mean [standard deviation] or median (interquartile range, 25th–75th percentile), as appropriate. *p* value, Fisher's exact test, unpaired *t* test or Mann-Whitney test between mild and moderate-to-severe stroke. *n*, number of participants; AIS, acute ischaemic stroke; NIHSS, National Institutes of Health Stroke Scale; MABP, mean arterial blood pressure; HR, heart rate; etCO<sub>2</sub>, end tidal CO<sub>2</sub>; CBFV, cerebral blood flow velocity; ARI, autoregulation index; A, affected hemisphere; U, unaffected hemisphere; LACS, lacunar stroke syndrome; PACS, partial anterior circulation stroke syndrome; TACS, total anterior circulation stroke syndrome. \* *p* < 0.05 vs. unaffected side. <sup>†</sup> *p* < 0.05 vs. greater NIHSS. <sup>§</sup> Outlier removed from dataset.

ARI between the AH and UH or between mild and moderate-to-severe stroke patients, including those with ARI <4 (Table 3).

Stroke severity had a significant correlation with some peripheral (mean and diastolic BP) and cerebral haemodynamic parameters (Table 4). For every 4-point NIHSS score increase, there was an increase in the UH of 2.8, 2.1 and 1.7 (cm•s<sup>-1</sup>) in systolic, mean and diastolic CBFV, respectively. In addition, a 4-point increase in NIHSS was associated with a 1.8 and 2.2 mm Hg reduction in mean and diastolic BP or 0.3 reduction in ARI in the UH. However, no significant correlation with stroke severity was observed for cerebral haemodynamic parameters in the AH (Table 4).

**Table 4.** Influence of stroke severity, assessed by NIHSS, on peripheral and cerebral haemodynamic parameters

|  | <i>n</i> | CC      | Regression coefficient | <i>p</i> value |
|--|----------|---------|------------------------|----------------|
| Peripheral parameters                    |          |         |                        |                |
| MABP (mm Hg)                             | 122      | -0.1944 | 102-0.46•NIHSS         | 0.03           |
| Systolic BP (mm Hg)                      | 122      | -0.0096 | 147-0.39•NIHSS         | 0.23           |
| Diastolic BP (mm Hg)                     | 121      | -0.1505 | 82-0.56•NIHSS          | <0.01          |
| HR (beats/min)                           | 121      | 0.1312  | 69+0.26•NIHSS          | 0.15           |
| etCO <sub>2</sub> (mm Hg)                | 88       | 0.0771  | 35+0.04•NIHSS          | 0.48           |
| Cerebral haemodynamics                   |          |         |                        |                |
| Mean CBFV (cm•s <sup>-1</sup> ) – A      | 104      | -0.005  | 42+0.013•NIHSS         | 0.96           |
| Mean CBFV (cm•s <sup>-1</sup> ) – U      | 113      | 0.1715  | 44+0.53•NIHSS          | 0.04           |
| Systolic CBFV (cm•s <sup>-1</sup> ) – A  | 104      | -0.009  | 65-0.03•NIHSS          | 0.93           |
| Systolic CBFV (cm•s <sup>-1</sup> ) – U  | 113      | 0.1873  | 70+0.70•NIHSS          | <0.05          |
| Diastolic CBFV (cm•s <sup>-1</sup> ) – A | 104      | 0.0340  | 27+0.07•NIHSS          | 0.73           |
| Diastolic CBFV (cm•s <sup>-1</sup> ) – U | 112      | 0.2147  | 28+0.43•NIHSS          | 0.02           |
| ARI (arbitrary units) – A                | 96       | -0.1388 | 5.1-0.05•NIHSS         | 0.18           |
| ARI (arbitrary units) – U                | 101      | -0.264  | 5.4-0.07•NIHSS         | <0.01          |

*p* value, Pearson or Spearman's rank test as appropriate. *n*, number of participants; CC, correlation coefficient; MABP, mean arterial blood pressure; HR, heart rate; etCO<sub>2</sub>, end tidal CO<sub>2</sub>; CBFV, cerebral blood flow velocity; ARI, autoregulation index; A, affected hemisphere; U, unaffected hemisphere; NIHSS, National Institutes of Health Stroke Scale.

## Discussion

This study demonstrated that overall many AIS patients had CA impairment, with an ARI below 4 during the first 48 h following stroke onset; 32% in the AH alone, 21% with bilateral impairment. There were no significant differences in ARI between stroke subtypes, defined by OCSF, or stroke severity, defined by NIHSS, except for a small reduction in ARI in the UH with increasing stroke severity. With respect to other measures of cerebral haemodynamics, no differences were observed for the AH by stroke subtype or severity. In the UH, TACS subtype and moderate-to-severe stroke severity was associated with increased CBFV.

### *Influence of Stroke Subtype*

Few studies have evaluated the effect of stroke subtype on CA in the acute phase [2, 4, 5], reporting bilateral impairment of CA with lacunar infarction and impaired CA predominantly in the AH in large vessel stroke [4, 5]. Nonetheless, definitive conclusions are limited by small sample sizes and methodological differences, and the present study allowed changes to be assessed in a large cohort of AIS patients using comparable methods. Our data support differences in CBFV between cortical (TACS) and subcortical (LACS) stroke, interestingly in favour of increased CBFV in the UH in TACS. A number of possible explanations could be put forward for this. First, subcortical stroke may be associated with small vessel disease, caused by diabetes and chronic hypertension [4, 5], and is more likely to lead to bilateral deterioration in cerebral haemodynamics [21]. Secondly, increased CBFV may be a response to the large vessel occlusion with recruitment of leptomeningeal collateral circulation from the UH. However, CBFV measured in the UH was similar to that reported in healthy individuals [17], and high levels of thrombolysis at 49% in the population studied may be associated with recanalization. Thirdly, CBFV in the UH may reflect cerebral steal, with there being previous

reports in stroke patients where perfusion to the UH is augmented [22]. Finally, associated ICA stenosis may have resulted in previous changes in cerebral haemodynamics, particularly collateral blood flow, though only 20% of patients had significant ICA stenosis greater than 50%, and all of these patients had different CBFV.

Nonetheless, despite CBFV changes, there was no significant effect of stroke subtype on CA, as assessed by the ARI. This is in contrast to some of the previous literature [2, 4, 5]. Apart from the non-stationarity of dynamic CA [23], other possibilities for the disparity include: previous studies on AIS patients containing smaller sample sizes, from selected populations, different methodology to define stroke subtype [4], and differences in parameters adopted to quantify CA [10].

#### *Influence of Stroke Severity*

Minor stroke [9], smaller stroke volumes [3] and/or successful thrombolytic therapy [8] have been associated with no adverse impact on CA. Whereas large artery stroke [2] with associated increased severity [3], unsuccessful thrombolysis [9] or haemorrhagic transformation [24] may be associated with impaired CA, particularly during the first few days of admission, and have an adverse impact on neurological outcome [25]. The present study demonstrated an overall non-significant reduction in ARI in moderate-to-severe compared to mild stroke. This could be due to the haemodynamic assessment occurring on average 11 hours later in the mild stroke patients. However, the increasing NIHSS score was weakly, but significantly, associated with deteriorating ARI in the UH only. Furthermore, differences in CBFV related to stroke severity were also only observed in the UH.

Stroke severity may be associated with cardiovascular complications, including autonomic dysfunction [26]. Though there was increased sympathetic activation (as evidenced by HR) in patients with moderate-to-severe stroke severity, we found no correlation between HR and NIHSS. In addition, there may be more dependency on baroreceptor sensitivity when CA is impaired [27], which may be diminished when there is increased sympathetic activity and higher HR, as when patients suffer stroke of greater severity [28, 29]. Finally, increased BP is well documented following stroke, though we found an inverse association between BP and NIHSS score, which is unsurprising in that more likely hypertensive LACS patients will have lower NIHSS scores. Nonetheless, our data should be interpreted with caution as there were fewer severe stroke patients included, and further studies of the effect of stroke severity on cerebral haemodynamics are warranted.

#### *Study Limitations*

There are a number of limitations to our study. First, though the OCSF is a widely used clinical classification, it does not consider underlying stroke aetiology, which may be more relevant in the potential impact on cerebral haemodynamics [30]. Secondly, NIHSS was not always taken on admission and at assessment, so maximum stroke severity could not be considered in further analysis. In addition, NIHSS was undertaken by several investigators. Thirdly, ARI was measured from spontaneous fluctuations between BP and CBF, though it is still to be determined whether small BP fluctuations are the best method for assessing CA [31]. The affected side had fewer good quality recordings and a poor goodness of fit to Tieck's model of CA, which could have added bias to some data sets. Finally, although, to our knowledge, this is currently the largest CA database of AIS patients to report cerebral haemodynamic changes, its size remains limited to definitely assess the effects of stroke subtype and severity.



## Conclusion

This large cohort demonstrated that cerebral haemodynamics represented by CBFV is significantly different according to stroke subtype and severity in the UH with higher values following TACS. This is a new finding that should be explored in future studies as a prognostic marker in this sub-population, particularly the impact of successful recanalization therapies. Our study corroborated previous findings that demonstrated an impairment of CA during the first 48 h; with this large sample, we could demonstrate that this impairment is not influenced by stroke subtype and is poorly associated with stroke severity in the UH.

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## Disclosure Statement

The authors declare that they have no conflicts of interest.

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