

1 **Cerebral Vasospasm affects Arterial Critical Closing Pressure**

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22

23 **Abstract**

24

25 The effect of cerebral vasospasm (CVS) following aneurysmal subarachnoid hemorrhage
26 (SAH) on critical closing pressure (CrCP) has not been fully delineated. Using cerebral
27 impedance methodology, we sought to assess the behavior of CrCP during CVS. As CrCP
28 expresses the sum of intracranial pressure (ICP) and vascular wall tension, we also explored
29 its role in reflecting changes in vascular tone occurring in small vessels distal to spasm.

30

31 This retrospective analysis was performed using recordings from 52 patients, diagnosed with
32 CVS through transcranial Doppler measurements. CrCP was calculated non-invasively using
33 arterial blood pressure and blood flow velocity. Outcome was assessed at both discharge and
34 3 months after ictus with the Glasgow Outcome Scale.

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36 The onset of CVS caused significant decreases in CrCP ($p=0.025$), without any observed
37 significant changes in ICP ($p=0.134$). Vasospasm induced asymmetry, with CrCP ipsilateral
38 to CVS becoming significantly lower than contralateral ($p=0.025$). Unfavorable outcomes
39 were associated with a significantly lower CrCP after the onset of CVS (discharge: $p=0.014$;
40 3 months post SAH: $p=0.020$).

41

42 CrCP is reduced in the presence of CVS in both temporal and spatial assessments. As ICP
43 remained unchanged during CVS, reduced CrCP most probably reflects a lower wall tension
44 in dilated small vessels distal to spasm.

45

46 **Key words:** critical closing pressure, subarachnoid hemorrhage, vasospasm, wall tension

47

48 **Introduction**

49 Cerebral vasospasm (CVS) is one of the most deleterious complications following
50 subarachnoid hemorrhage (SAH)¹⁻³, being thought to disturb cerebral haemodynamics,
51 leading often to hypoperfusion³⁻⁵ and contributing to delayed cerebral ischemia (DCI)⁶⁻⁸.
52 However, the stenosis of the spastic artery alone cannot fully explain the subsequent
53 development of DCI, as not all patients with CVS, detected either radiologically or with
54 transcranial Doppler (TCD), develop DCI⁸⁻¹⁰.

55 For this reason, assessment of changes in the cerebral microvasculature distal to spastic
56 vessels may be important. However, previous studies have yielded conflicting results.
57 Positron emission tomography and radioisotope studies have reported findings of maximal
58 vasodilatation^{11,12} and an impaired vasoreactivity distal to spastic segments^{13,14}, whereas
59 another experimental study reported narrowing of intraparenchymal arterioles post SAH¹⁵.
60 Moreover, both TCD and Near Infrared Spectroscopy techniques have demonstrated that an
61 early onset of dysautoregulation before vasospasm correlates with the occurrence of DCI but
62 not with a worse outcome¹⁶, unless autoregulatory failure spreads to both hemispheres.¹⁷ This
63 may further complicate our understanding of the microvasculature's role in SAH.

64 A parameter that could aid in this situation is critical closing pressure (CrCP), which
65 estimates the theoretical lowest value of arterial blood pressure (ABP) that is adequate for
66 maintaining cerebral blood flow¹⁸. Any value of ABP below this threshold will result in a
67 collapse of small vessels, leading to cessation of blood flow. CrCP has been modelled as the
68 sum of intracranial pressure (ICP) and vascular wall tension (WT) of small vessels¹⁹.
69 Therefore, observation of how CrCP and WT vary can provide an insight into the dynamics
70 of cerebral resistive vessels and its behavior in pathological states like CVS.

71 The use of CrCP in clinical practice has been restricted by methodological drawbacks,
72 namely due to presence of difficult to interpret negative CrCP values in conditions with
73 increased cerebral blood flow velocity²⁰⁻²³, including CVS²⁴. We have recently described a
74 method for estimating CrCP based on cerebrovascular impedance^{25,26}, which has
75 demonstrated a good correlation with traditional methods in many clinical conditions^{26,27},
76 without yielding negative values.

77 The primary aim of our study was to describe the behavior of CrCP during CVS. First,
78 because the state of the microvasculature in SAH is unclear, and with CrCP being related to
79 vasomotor tone, we examined whether any changes in CrCP presented during CVS could be
80 indicative of changes in the microvascular wall tension distal to spasm. Secondly, we
81 explored the relationship of CrCP with autoregulation and how this relationship becomes
82 affected with CVS. Finally, we also explored the existence of any association of CrCP and
83 outcome following SAH.

84

85 **Methods**

86 **Patients**

87 We retrospectively analyzed prospectively collected data from a group of 98 aneurysmal
88 SAH patients admitted to the Neurocritical Care Unit of Addenbrooke's Hospital, Cambridge
89 (June 2010-January 2012)^{16,28}. Approval of the study was given by the Addenbrooke's
90 Research Ethics Committee. Patients gave written informed approval for the study or in case
91 they were incapacitated, the written consent was signed from next-of-kin. The guidelines
92 governing the prospective study on which this retrospective analysis is based on have been
93 reported previously by Budohoski et al¹⁶, where the cohort was assessed from the aspect of
94 early changes in cerebral autoregulation.

95 Bilateral TCD measurements at the temporal window (depth of 40-60 mm) were used to
96 identify CVS in a total of 52 patients [median age: 52 years (interquartile range 45-60);
97 females/males: 36/16] who had a mean blood flow velocity (FV) in the middle cerebral artery
98 (MCA) exceeding 120 cm/s, with a concomitant Lindegaard Ratio (LR) of above 3.0 on
99 TCD²⁹. Overall patient characteristics are presented on Table 1 (Section A). The median
100 onset of CVS was 6 days post SAH. Cerebral perfusion was optimized with the use of
101 hypertension, hypervolemia, and hemodilution as part of the triple-H therapy in patients who
102 developed DCI (31/52 of CVS patients)^{16,30}. The Glasgow Outcome Scale (GOS) was used
103 for assessing outcome at both discharge from hospital and 3 months post SAH.

104

105 **Monitoring and Data Analysis**

106 Monitoring periods included recordings of ABP, ICP and bilateral FV, performed every 1-2
107 days¹⁶. ABP was measured either from the radial artery using a pressure monitoring kit
108 (Baxter Healthcare, Deerfield, IL, USA), or non-invasively with a Finapres 2300 finger
109 plethysmograph (Ohmeda, Amsterdam, The Netherlands) zeroed at the heart level in all
110 patients. Patients were supine with the head of the bed raised 30-45 degrees. Patients
111 requiring ventriculostomy for hydrocephalus (N=21) had an external ventricular drain (EVD),
112 which was used for drainage of cerebrospinal fluid when open and for ICP measurements
113 when closed. The external drainage was closed during the TCD monitoring period,
114 preventing possible interference of high cerebrospinal compliance (open EVD) with cerebral
115 hemodynamics. Out of these 21 patients, 14 had a full set of measurements both before and
116 during CVS that were used for analysis of change in ICP during CVS. Doppler monitoring of
117 FV was performed bilaterally at MCAs, with the use of a DopplerBox (DWL Compumedics,
118 Singen, Germany) and a head positioning device (Lam Rack, DWL Compumedics) via the
119 temporal window at a depth of 45-60 mm. The raw data signals were recorded at sampling

120 frequency of 200 Hz using ICM+ software (Cambridge Enterprise, Cambridge, UK,
121 <http://www.neurosurg.cam.ac.uk/icmplus/>). Mean values of signals were calculated in ICM+
122 by averaging values in a 10-second time window and then secondarily averaging them over
123 whole monitoring time (20-40 min). Heart rate was calculated using spectral position of the
124 peak associated with the first harmonic of ABP.

125 Cerebral autoregulation was assessed with a TCD-derived autoregulation index, Sxa,
126 calculated as a moving correlation coefficient between ABP and systolic FV, from a 300-
127 second window with averaging every 10 seconds¹⁶.

128

129 **Estimation of Critical Closing Pressure**

130 CrCP was estimated with the impedance methodology^{25,26}, using a non-invasive version
131 requiring signals of ABP and TCD FV³¹:

$$132 \quad CrCP = ABP \cdot \left[1 - \frac{1}{\sqrt{(CVR \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}} \right]$$

133 CVR stands for cerebrovascular resistance with Ca representing arterial compliance of the
134 cerebral bed. Calculation of CVR and Ca can be performed with algorithms based on
135 measurements of FV and ABP, presented in previous studies^{32,33}. HR represents heart rate
136 (beats/s).

137 Please see the Appendix for further details regarding non-invasive CrCP methodology.

138

139 **Statistical analysis**

140 The IBM SPSS Statistics 20 package (Armonk, NY, USA) was used for the statistical
141 analysis. The Shapiro–Wilk test was used to confirm normal distribution of the samples.

142 Results are presented in a mean value \pm standard deviation (SD) format. Bivariate
143 correlations were used, with R being the Pearson correlation coefficient. The level of
144 significance (p-value) was set at 0.05.

145 For analysis of CrCP in cases of unilateral CVS, the TCD recordings from the side ipsilateral
146 to CVS were used, whereas when bilateral CVS was present, the analysis included averaging
147 of both sides.

148 Temporal and spatial comparisons were used to assess how CrCP was affected by the
149 presence of CVS, performed with paired samples T-tests. In temporal comparison, the cohort
150 of CVS patients was dichotomized in time, with comparison of averaged periods before and
151 during CVS, based on the TCD onset of CVS for each patient. Spatial analysis included
152 bilateral comparisons (ipsilateral-contralateral to CVS). Both temporal and spatial
153 comparisons were made using data of patients with recordings both before and during CVS
154 (37 patients out of the total 52; Figure 1).

155 Autoregulation analysis included averaged periods of calculated autoregulatory index Sxa,
156 before and during CVS, with the relationship to CrCP being explored through correlation to
157 the respective averaged periods of CrCP.

158 Outcome analysis consisted of comparisons between favorable (GOS: good recovery,
159 moderate disability) vs unfavorable (GOS: severe disability, vegetative state, death)
160 outcomes, for the patients who had recordings both before and during CVS (N=37).
161 Comparisons included then averaged recordings of CrCP and FV for several days both before
162 and after the CVS onset. The outcome scores were collected at discharge and at 3 months
163 after injury. Binary logistic regression models were used for analysing the association of
164 CrCP to outcome. Section B of Table 1 presents a comparison between patients of favorable

165 and unfavorable outcomes, with the latter presenting a significantly worse WFNS score and a
166 higher percentage of occurrences of hydrocephalus and DCI.

167 The rest of SAH cohort that did not develop CVS (46 out of 98 patients) was used as a
168 control group, where CrCP was averaged for the whole monitoring period.

169

170 **Results**

171 **Effects of vasospasm on critical closing pressure**

172 Mean values of measured parameters and CrCP before and during CVS are presented in
173 Table 2. CrCP became significantly lower during CVS, decreasing by 14.7% after the onset
174 of CVS ($p=0.025$). FV was significantly increased during CVS ($p<0.001$), as was ABP
175 ($p<0.001$).

176 ICP did not significantly change during CVS, even though a tendency to decrease was
177 observed after the onset of CVS (before CVS: 13.55 ± 4.04 mm Hg; after onset of CVS:
178 11.04 ± 5.78 mm Hg; $p=0.134$, $N=14$). Changes in ICP were not correlated to changes in
179 CrCP from before to during vasospasm (absolute changes; $p=0.379$, $N=14$).

180 Changes in CrCP observed in time after SAH were not associated with changes in FV, as the
181 absolute difference of CrCP before and during CVS was not correlated with the respective
182 absolute difference of FV ($R=-0.227$; $p=0.177$). The independence of CrCP and FV was
183 further confirmed with an overall absence of correlation between them during CVS
184 ($p=0.148$).

185 No significant interhemispheric difference could be found in either CrCP or FV before the
186 onset of CVS ($p=0.394$ and $p=0.143$ respectively). However, the presence of CVS reduced
187 CrCP in both hemispheres and induced asymmetry, with CrCP ipsilateral to CVS becoming

188 significantly lower than contralateral CrCP during to CVS ($p=0.025$; Figure 2). Ipsilateral FV
189 was significantly higher than contralateral FV during CVS (154.13 ± 44.94 vs 104.45 ± 40.58
190 cm/s; $p<0.001$).

191 Interhemispheric changes in CrCP were not correlated to changes in FV during CVS
192 ($R=0.056$; $p=0.763$). The interhemispheric asymmetry of CrCP was not constant across the
193 days post SAH, with the biggest differences being on days 11 and 12 (Table 3).

194 Comparison of CrCP values of CVS patients to a control group, consisting of the rest 46 SAH
195 patients (out of a total 98) that did not develop CVS, demonstrated a significantly lower CrCP
196 in CVS cases (CrCP after the onset of vasospasm in CVS patients: 40.70 ± 16.72 mm Hg;
197 CrCP in SAH patients without no presence of vasospasm: 34.67 ± 9.77 mm Hg; $p=0.015$). No
198 significant difference could be found between the control SAH group and the averaged period
199 before the presence of vasospasm for the CVS patients ($p=0.659$).

200

201 **Autoregulation**

202 Sxa and CrCP were inversely correlated before CVS ($R=-0.329$; $p=0.043$). Autoregulation
203 presented signs of impairment during CVS, as shown by a significantly increased Sxa (from
204 0.14 ± 0.18 to 0.22 ± 0.15 ; $p=0.023$). During CVS, there was no correlation between Sxa and
205 CrCP ($R=0.122$; $p=0.471$).

206

207 **Outcome**

208 Compared to patients with favorable outcome ($N=29$), unfavorable cases ($N=8$) had a
209 significantly lower CrCP during the CVS period, with outcome assessed both at discharge

210 (p=0.014, Figure 3A) and at 3 months post SAH (p=0.020, Figure 3B). No association was
211 found between CrCP before CVS onset and outcome (p>0.05 for all).

212 Adjusting for FV during CVS, binary logistic analysis (with independent parameters CrCP
213 and FV) indicated a lower CrCP to remain significantly and independently to FV associated
214 with unfavorable outcome (Table 4).

215

216 **Discussion**

217 Overall, during cerebral vasospasm we observe significant decrease in CrCP. This could be
218 seen both in temporal assessment where the onset of CVS resulted in a decrement of CrCP,
219 and in spatial investigation, where CVS caused an interhemispheric CrCP difference, with a
220 lower CrCP ipsilateral to spasm. This could be also seen when comparing to a control group
221 of SAH patients without presence of CVS: whereas before the onset of CVS there was no
222 difference between patients that later developed CVS and the control group, after the onset of
223 CVS, CrCP became significantly lower in comparison to the control group.

224 Because CrCP is the sum of ICP and WT¹⁹, any observed changes could be the end result of
225 alterations in either variable. The onset of CVS did not cause any significant changes in ICP,
226 which remained at relatively low levels. Therefore, the observed changes in CrCP could be
227 reflecting changes in WT, where a reduced WT would be signifying a reduced vasomotor
228 tone and dilated vessels. This preliminary inference would be in agreement with previous
229 studies demonstrating dilated parenchymal small arteries and arterioles in the low perfusion
230 area distal to spasm^{11-14,34}, attributed to a possible autoregulatory response^{35,36}.

231 The behavior of the microvasculature during CVS has previously attracted considerable
232 interest, although both clinical and experimental studies have produced conflicting results¹¹⁻

233 ¹⁵. A better understanding of microcirculatory changes may lead to better ways of
234 maintaining adequate local perfusion pressure, which otherwise gets significantly affected by
235 the stenosis³⁻⁵. Lowering of CrCP during spasm for most investigators is counterintuitive;
236 spasm increases tension of conductive vessels, therefore CrCP should rather rise than
237 decrease. But CrCP describes better the state of resistive arterioles rather than conductive
238 vessels¹⁹. Spasm in conductive vessels decreases effective cerebral perfusion pressure at the
239 level of the resistive arterioles, causing dilation, a decrease in wall tension, and decreases in
240 CrCP.

241

242 **Clinical significance**

243 The changes in CrCP occurred despite the initiation of triple-H therapy, which includes
244 raising of ABP³⁰. Normally, arterial hypertension causes vasoconstriction^{35,37}, which is
245 known to lead to a higher CrCP through an increased WT²⁶. Therefore, the observed
246 decreases in CrCP could signify a strong dilatatory effect of proximal vasospasm on distal
247 microcirculation.

248 A lower CrCP after the onset of CVS was associated with an unfavorable outcome, in
249 contrast to FV. As the level of FV is of high importance in TCD-assessed vasospasm^{23,29,36},
250 this preliminary finding denoting the relationship of CrCP with FV and outcome deserves
251 further discussion. With CrCP appearing to express changes in microcirculation, this finding
252 could enhance its clinical importance, potentially denoting its role as a quantitative surrogate
253 marker of dilated vessels being associated with a worse outcome.

254 Furthermore, before the CVS onset an inverse association was found between CrCP and
255 autoregulation: a lower CrCP being linked with a higher Sxa or worsening of autoregulation.
256 This relationship could be explained by an apparent reduced pressure reactivity due to vessels

257 becoming dilated and therefore having a lower vasomotor tone, expressed with a reduced
258 CrCP. A similar relationship between WT and autoregulation has been previously observed
259 in traumatic brain injury³⁸.

260 **Advantages of impedance-based CrCP**

261 The main advantage of impedance CrCP is that its renderings in SAH patients agreed with
262 the findings of an earlier study using two traditional CrCP methods²⁴, without presenting
263 though any negative values for this pathology, as has been also verified with this estimation
264 method in both experimental and clinical scenarios.^{26,27,31,38}.

265 Despite CrCP calculations being based on FV-derived information, the changes in CrCP
266 during CVS were independent from changes in FV, therefore not being artificially driven by
267 increasing FV²⁴ but rather being representative of changes in the physiology of the
268 microvasculature. Most importantly the calculations with our method were not affected by
269 the diameter change of the insonated vessel, as the calculation of CrCP is independent of the
270 insonated vessel's unknown cross-sectional area (please see Appendix)^{26,33}.

271 All of the above makes the new impedance based measures of CrCP superior to the
272 traditional methods and suitable for use in clinical practice, particularly in SAH patients
273 where vasospasm has occurred.

274

275 **Limitations**

276 Calibration of ABP at heart-level instead of brain-level could be considered a confounding
277 factor in this study, leading to an overestimation of ABP at the level of the insonated vessel³⁹,
278 potentially affecting therefore impedance CrCP calculations. However, this study explored
279 the changes in CrCP caused by the presence of vasospasm, rather than assessing absolute

280 values of CrCP. Therefore the use of this ABP calibration, consistent throughout the
281 measurements with patients having an unchanged 30-45 degrees head up, could be
282 considered as adequate for the purposes of this study.

283 In contrast to continuous ABP measurements, TCD recordings were performed for short
284 periods (30 to 60 minutes) for every patient on a day-to-day basis¹⁶. This means that
285 calculation of CrCP was only possible when the recordings of ABP and FV were combined
286 during these short periods. This is a known limitation of the TCD methodology at present,
287 and one that can only be overcome by the advent of new self-focusing TCD probes.
288 Nevertheless, these ‘snapshots’ of CrCP were deemed adequate for the aims of the study¹⁶.

289 The overall number of patients may pose a limitation for this study. However, despite the
290 small number of patients, the results were able to: a) present an agreement with the results of
291 a past study²⁴ b) demonstrate at the same instance the strength of the reliable impedance
292 CrCP method and c) preliminary indicate an association of CrCP with a worse outcome,
293 independently to FV, which consists of a widely used marker of CVS. Furthermore, the lack
294 of a multivariate regression model for outcome assessment is a limitation for this study. A
295 prospective study with a larger number of patients will be able to further explore the
296 relationship of CrCP with outcome, through a multivariate regression analysis taking under
297 consideration other parameters such as age, sex, WFNS score etc. With a larger sample of
298 SAH patients a further analysis could investigate whether a specific threshold for CrCP
299 predicting a worse outcome could be identified.

300 Furthermore, the small number of patients with ICP measurements for assessing changes
301 occurred during CVS could be considered as a limitation, mainly attributed to the fact that
302 SAH patients do not routinely receive intracranial monitoring¹⁶. However, similar findings

303 regarding the effect of CVS on ICP have been presented before, therefore confirming our
304 results.²⁴

305

306 **Conclusions**

307 The presence of vasospasm significantly reduced CrCP, as seen in temporal assessment
308 where the onset of vasospasm resulted in a decrement of CrCP, and in spatial assessment,
309 where vasospasm caused an interhemispheric CrCP difference, with a lower CrCP ipsilateral
310 to spasm.

311

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325

326 **Disclosure/Conflict of Interest**

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487 **Titles and legends to figures**

488 **Figure 1:** Dichotomization of patients into study groups, considering the aims of each
489 comparison and the availability of monitored signals. From a cohort of 98 patients with
490 subarachnoid hemorrhage (SAH), patients that developed cerebral vasospasm (CVS) were
491 studied (52). From this group, the intracranial pressure (ICP) part consisted of a total of 21
492 patients with monitoring of ICP. Out of these 21 patients, 14 had ICP measurements both
493 before and during CVS and were used for assessing changes in ICP following the onset of
494 CVS. For the CrCP part, 37 patients were used for CrCP comparisons, after fulfilling the
495 criteria of full measurements, regarding presence of arterial blood pressure (ABP) and
496 bilateral transcranial Doppler flow velocity (FV) both before and during CVS.

497 **Figure 2:** Bilateral comparison of critical closing pressure (CrCP) for periods before and
498 during vasospasm (CVS): CVS causes asymmetry with ipsilateral CrCP becoming
499 significantly lower than contralateral, whereas in contrast, no significant interhemispheric
500 difference was found before CVS. Error bars represent +/- 2 standard errors.

501 **Figure 3:** Association of critical closing pressure (CrCP) after the onset of vasospasm (CVS)
502 with outcome of patients (N=37) at both discharge (**A**) and 3 months post subarachnoid
503 hemorrhage (SAH) (**B**). In both time points, unfavorable outcome cases presented a
504 significantly lower CrCP, in comparison to favorable cases. Error bars represent +/- 2
505 standard errors.

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511 **Tables**

512

513 **Table 1** Characteristics of patients with cerebral vasospasm, consisting of a subgroup of the
 514 total cohort of patients with subarachnoid hemorrhage. Section A presents overall
 515 characteristics, with Section B comparing characteristics of patients with favorable and
 516 unfavorable outcomes.

517

Section	Variable		Value	
	Number of Patients, n		52	
	Age, median years (IQR)		52 (45-60)	
	Sex, female/male		36/16	
	WFNS grade, median		Modified Fisher grade, median	
A	1, n	16	1, n	9
	2, n	16	2, n	6
	3, n	2	3, n	29
	4, n	12	4, n	8
	5, n	6	-	
	Aneurysm location, n			
	ACA	2	MCA	11
	AChA	3	PCoMA	16
	ACoMA	14	PCA	0
	BA	1	PICA	1
	ICA	3	VBJ	0
	Clipping/coiling, n	39/17	Re-bleeding, n	0
	Surgical Infarcts, n	8	Hydrocephalus, n	28

Outcome (N=37 patients)				
median GOS at 3 months		5 (IQR: 4-5)		
Favorable vs. Unfavorable				
Parameter	Favorable	Unfavorable	p-value	
Number of patients, n	29	8	-	
B Age, median years (IQR)	54 (45-62)	53 (49-63)	0.732	
Sex, female/male	21/8	4/4	-	
WFNS grade, median	2	4	0.003*	
Modified Fisher grade, median	3	2	0.332	
Hydrocephalus	16	6	-	
DCI	15	6	-	

518 **Abbreviations:** **ACA:** anterior cerebral artery; **AChA:** anterior choroidal artery; **ACoMA:**
519 anterior communicating artery; **BA:** basilar artery; **ICA:** internal carotid artery; **IQR:**
520 interquartile range; **MCA:** middle cerebral artery; **PCA:** posterior cerebral artery; **PCoMA:**
521 posterior communicating artery; **PICA:** posterior inferior cerebellar artery; **VBJ:**
522 Vertebrobasilar junction; **WFNS:** scale of World Federation of Neurosurgical Societies
523 **GOS:** Glasgow Outcome Scale; *: significant difference – independent samples test.

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530 **Table 2** Comparison of mean values and standard deviations (mean \pm SD) of parameters
531 before and during cerebral vasospasm (Paired Samples T-test)

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N=37	Before CVS	During CVS	p-value
CrCP [mm Hg]	40.70 \pm 16.72	34.71 \pm 9.85	P=0.025
FV [cm/s]	80.38 \pm 24.21	153.41 \pm 42.99	P<0.001
ABP [mm Hg]	90.33 \pm 14.64	103.39 \pm 18.78	P<0.001

533

534 **Abbreviations:** CVS, cerebral vasospasm, **CrCP**, critical closing pressure; **FV**, blood flow
535 velocity; **ABP**, arterial blood pressure. Both CrCP and FV parameters refer to ipsilateral to
536 CVS measurements

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549 **Table 3** Interhemispheric difference in CrCP, patient-averaged by day post-SAH from the
 550 onset of spasm and onwards (median onset for all patients: 6 days post SAH). Based on
 551 clinical assessment, the monitoring time was not equivalent for all patients, therefore the
 552 number of available patients analyzed for each day is denoted.

553

Days	Number	ΔCrCP
post SAH	of Patients	[mean\pmSD; mm Hg]
6	median onset of spasm	
7	20	0.66 \pm 5.79
8	21	3.24 \pm 7.37
9	24	2.79 \pm 5.68
10	20	1.62 \pm 8.69
11	12	6.87 \pm 5.27
12	11	5.14 \pm 6.77
13	10	1.75 \pm 6.60

554

555 **Abbreviations:** CrCP, critical closing pressure; Δ CrCP, interhemispheric differences in
 556 CrCP; SAH, subarachnoid hemorrhage

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559 **Table 4:** Binary Logistic Regression Model for predicting outcome.

560

Outcome	Parameters	B (standard	Wald	p	OR	95% CI for
(Favorable vs Unfavorable)		Error)				OR
Discharge	CrCP	0.099 (0.045)	4.82	0.028	1.105	1.011-1.207
	FV	-0.010 (0.008)	1.702	0.192	0.990	0.974-1.005
3 months	CrCP	0.104 (0.052)	3.991	0.046	1.110	1.002-1.229
	FV	-0.011 (0.009)	1.524	0.217	0.989	0.972-1.007

561

562 **Abbreviations:** CrCP, critical closing pressure; FV, flow velocity; OR, odds ratio; CI,
563 confidence interval.

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573 **Appendix**

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575 **Calculation of non-invasive CrCP**

576

577 The basis of non-invasive CrCP is a multi-parameter invasive model, derived from the
578 concept of impedance^{25,26}:

579

580
$$CrCP = ABP - \frac{CPP}{\sqrt{(CVRi \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}} \quad (1)$$

581

582 The invasive parts requiring ICP measurements are CPP (calculated as ABP-ICP) and
583 cerebrovascular resistance (CVRi), approximated as⁴⁰:

584

585
$$CVRi = \frac{CPP}{FV \cdot S_a} \left[\frac{mm \ Hg \cdot s}{cm^3} \right]$$

586

587 The parameter S_a in the denominator represents the unknown cross-sectional area of the
588 insonated vessel.

589 Ca can be estimated as^{32,33}:

590

591
$$Ca = \frac{CaBV1 \cdot Sa}{A1} \left[\frac{cm^3}{mm \ Hg} \right]$$

592

593 A1: fundamental harmonic amplitude of ABP; CaBV1: amplitude of the fundamental
594 harmonic of cerebral arterial blood volume (CaBV), derived by using a 10-second discrete
595 Fourier transformation of CaBV's time series. CaBV is approximated by integrating FV pulse
596 waveform with the beat-to-beat mean removed^{32,33}.

597 The product of Ca and $CVRi$ in eq. (1) cancels out the parameter S_a , as has been described in
598 the impedance methodology²⁶.

599 Approximating $CrCP$ non-invasively, we used the $CrCP$ formula, substituting CPP with ABP ,
600 with $CVRi$ being now approximated non-invasively as⁴⁰:

601

$$602 \quad CVR = \frac{ABP}{FV \cdot S_a} \left[\frac{mm \ Hg \cdot s}{cm^3} \right]$$

603

604 With these substitutions, the non-invasive model of impedance $CrCP$ is now rendered as³¹:

$$605 \quad CrCP = ABP \cdot \left[1 - \frac{1}{\sqrt{(CVR \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}} \right] \quad (2)$$

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