**Supplemental Digital Content 4**

**Blood pressure and end-tidal carbon dioxide ranges during aneurysm occlusion and neurological outcome after an aneurysmal subarachnoid hemorrhage**

Annemarie Akkermans, MD1

Judith A. van Waes, MD, PhD1

Linda M. Peelen, PhD1,2

Gabriel J. Rinkel, MD, FRCP(E)3

Wilton A. van Klei, MD, PhD1

1 Department of Anesthesiology, University Medical Center Utrecht, Utrecht University, The Netherlands
2 Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, The Netherlands
3 Department of Neurology and Neurosurgery, Brain Centre Rudolf Magnus, University Medical Center Utrecht, Utrecht University, The Netherlands

**Correspondence to:**

A. Akkermans, MD; Email: a.akkermans@umcutrecht.nl

**Table 1. Number of missing data**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable  | N | Variable | N |
| Age  | 0 | Mean ETCO2 during intervention | 3 |
| Sex  | 0 | Pre-induction oxygenation  | 119 |
| BMI  | 545 | Duration of intervention  | 224 |
| ASA  | 18 | Duration of anesthesia  | 0 |
| Myocardial infarction  | 4 | Ephedrine  | 0 |
| Congestive heart failure  | 29 | Phenylephrine  | 0 |
| Cerebrovascular accident  | 5 | Norepinephrine  | 0 |
| Diabetes mellitus  | 15 | Dopamine  | 0 |
| Hypertension  | 6 | Dobutamine  | 0 |
| Vascular disease  | 15 | Post-intervention neurological decline  | 110 |
| Pulmonary disorder  | 15 | Complications |  |
| History of Smoking  | 129 |  Re-bleed  | 0 |
| Use of anticoagulants on admission  | 98 |  Cerebral ischemia %) | 0 |
| Use of statins on admission  | 98 |  Hydrocephalus  | 0 |
| Use of antihypertensive drugs on admission  | 28 |  Cerebral edema  | 0 |
| WFNS on admission  | 9 |  Convulsion  | 0 |
| WFNS preoperative  | 314 |  Other intracranial complication  | 0 |
| Type of intervention  | 0 |  Extracranial complication  | 0 |
| Day of intervention  | 0 |  Hypernatremia  | 18 |
| Pre-intervention WFNS  | 134 |  Hyponatremia  | 41 |
| Pre-intervention intubation  | 7 |  Anemia  | 61 |
| Number of GA before intervention  | 3 |  Hypomagnesemia  | 290 |
| Number of GA after intervention  | 2 |  Hyperglycemia  | 77 |
| CSF drainage  | 9 |  Hypoglycemia  | 68 |
| Coiling attempt prior to clipping  | 3 | Length-of-stay  | 30 |
| Pre-induction Mean MAP  | 216 | GOS discharge  | 12 |
| Mean MAP during intervention | 0 | GOS 3 months  | 261 |

*ASA: American Society of Anesthesiologist Physical Status Classification. BMI: body mass index. CSF: cerebral spinal fluid. ETCO2: end-tidal carbon dioxide concentration. GA: general anesthesia. GOS: Glasgow Outcome Scale. MAP: mean arterial blood pressure. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage (1 = optimal score, 5 = worst score).*

**List of variables used for imputation**

*All observed information, except information on the independent variables (TWA-AUC and mean end-tidal carbon dioxide concentration (ETCO2) and mean arterial blood pressure (MAP) was used for multiple imputation.*

Age

Height

Weight

Sex

ASA class

History of

* Myocardial infarction
* Congestive heart failure
* Cerebrovascular accident
* Diabetes mellitus
* Hypertension
* Vascular disease
* Pulmonary disorder
* Polycystic kidney disease
* Arrhythmia
* Pacemaker or implantable cardioverter defibrillator (ICD)
* Smoking

Use of anticoagulants on admission

Use of statins in admission

Use of antihypertensive drugs on admission

World Federation of Neurological Surgeons Grading System Score on admission and prior to the intervention

Location of aneurysm

Type of intervention

Day of intervention

Cerebral spinal fluid drainage

Pre-intervention intubation

Number of times of general anesthesia during admission, prior to and after occlusion of the aneurysm

Intubation prior to the intervention

Coiling attempt prior to clipping

Pre-induction mean of mean arterial blood pressure (MAP)

Pre-induction oxygenation

Duration of intervention and general anesthesia.

Amount of ephedrine, phenylephrine, norepinephrine, dopamine, dobutamine administered during the intervention

Postoperative neurological decline

Complications (re-bleed, cerebral ischemia, hydrocephalus, cerebral edema, convulsions, other intracranial complications, hypernatremia, hyponatremia, anemia, hypomagnesemia, hyperglycemia, hypoglycemia, other extracranial complications)

Length of stay

Glasgow outcome scale at discharge and at three months

**Table 2 Results from the complete case analyses versus analyses on the imputed data for the association between time-weighted average area-under-the curve thresholds and neurological outcome at discharge**

|  |  |  |
| --- | --- | --- |
| **Threshold and categories**N = number of patients with TWA-AUC > 0CI and sign. level for p-value are reported per threshold † | **Poor outcome at discharge****Complete cases****Univariable analyses** | **Poor outcome at discharge Multiple imputation** **Univariable analyses** |
|   | RR (CI) | p-value  | RR (CI)  | p-value |
| ETCO2 < 30 mmHg (N = 405; CI 98.8%; sign. p < 0.013) |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 1.01 (0.62 - 1.63) | 0.980 | 0.99 (0.61 - 1.61) | 0.965 |
|  Q 0-0.75 (0-0.8 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (0.8-6.5 mmHg ·min) | 0.84 (0.46 - 1.53) | 0.467 | 0.82 (0.45 - 1.49) | 0.407 |
|  Q 0.9-1.0 (6.5-57.2 mmHg ·min) | 0.88 (0.45 - 1.71) | 0.650 | 0.86 (0.44 - 1.67) | 0.576 |
| ETCO2 < 35 mmHg (N = 1022, CI 99.3%; sign. p < 0.007) |   |   |   |  |
|  Q 0 ( 0 mmHg ·min) | 2.42 (1.17 - 5.01) | 0.001\* | 2.39 (1.15 - 4.96) | 0.001\* |
|  Q 0-0.1 (0-1.2 mmHg ·min) | 1.22 (0.47 - 3.16) | 0.593 | 1.21 (0.46 - 3.21) | 0.612 |
|  Q 0.1-0.25 (1.2-9.8 mmHg ·min) | 1.15 (0.67 - 1.99) | 0.487 | 1.15 (0.67 - 1.98) | 0.507 |
|  Q 0.25-0.5 (9.8-23.8 mmHg ·min)  | 1.13 (0.71 - 1.82) | 0.492 | 1.13 (0.71 - 1.81) | 0.493 |
|  Q 0.5-0.75 (23.8-39.5 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (39.5-52.6 mmHg ·min) | 0.90 (0.52 - 1.56) | 0.608 | 0.89 (0.51 - 1.55) | 0.590 |
|  Q 0.9-1.0 (52.6-107.1 mmHg ·min) | 0.87 (0.46 - 1.64) | 0.557 | 0.85 (0.45 - 1.62) | 0.517 |
| ETCO2 < 40 mmHg (N = 1072, CI 99.3%; sign. p < 0.007)  |   |   |   |  |
|  Q 0 ( 0 mmHg ·min) | 2.23 (0.68 - 7.25) | 0.068 | 2.17 (0.65 - 7.23) | 0.083 |
|  Q 0-0.1 (0-41.9 mmHg ·min) | 1.71 (0.88 - 3.35) | 0.031 | 1.70 (0.86 - 3.34) | 0.035 |
|  Q 0.1-0.25 (41.9-56.5 mmHg ·min) | 1.36 (0.79 - 2.33) | 0.131 | 1.34 (0.78 - 2.30) | 0.148 |
|  Q 0.25-0.5 (56.5-71.8 mmHg ·min)  | 1.33 (0.83 - 2.13) | 0.107 | 1.31 (0.82 - 2.10) | 0.122 |
|  Q 0.5-0.75 (71.8-88.0 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (88.0-101.3 mmHg ·min) | 0.95 (0.54 - 1.66) | 0.808 | 0.94 (0.54 - 1.64) | 0.771 |
|  Q 0.9-1.0 (101.3-156.3 mmHg ·min) | 0.90 (0.48 - 1.71) | 0.683 | 0.89 (0.47 - 1.68) | 0.626 |
| ETCO2 < 45 mmHg (N= 1074, CI 99.3%; sign. p < 0.007) |   |   |   |  |
|  Q 0 ( 0 mmHg ·min) | 1.90 (0.56 - 6.44) | 0.160 | 1.87 (0.54 - 6.54) | 0.178 |
|  Q 0-0.1 (0-90.3 mmHg ·min) | 1.89 (0.97 - 3.67) | 0.010 | 1.88 (0.96 - 3.69) | 0.011 |
|  Q 0.1-0.25 (90.3-105.7 mmHg ·min) | 1.36 (0.79 - 2.34) | 0.124 | 1.36 (0.79 - 2.34) | 0.129 |
|  Q 0.25-0.5 (105.7-121.2 mmHg ·min)  | 1.31 (0.82 - 2.11) | 0.123 | 1.32 (0.82 - 2.11) | 0.115 |
|  Q 0.5-0.75 (121.2-137.5 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (137.5-151.1 mmHg ·min) | 0.98 (0.56 - 1.70) | 0.918 | 0.98 (0.56 - 1.70) | 0.912 |
|  Q 0.9-1.0 (151.1-206.2 mmHg ·min) | 0.90 (0.47 - 1.70) | 0.664 | 0.89 (0.47 - 1.69) | 0.634 |
| MAP < 60 mmHg (N = 166, CI 98.3%; sign. p < 0.017) |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 0.84 (0.45 - 1.56) | 0.516 | 0.92 (0.50 - 1.71) | 0.767 |
|  Q 0-0.9 (0-0.11 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.9-.1.0 (0.11-7 mmHg ·min) | 0.85 (0.39 - 1.85) | 0.628 | 0.86 (0.39 - 1.85) | 0.641 |
| MAP < 70 mmHg (N = 503, CI 99.0%; sign. p< 0.010)  |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 0.71 (0.48 - 1.06) | 0.026 | 0.81 (0.53 - 1.22) | 0.181 |
|  Q 0-0.5 (0-0.02 mmHg ·min) | 0.72 (0.21 - 2.44) | 0.497 | 0.71 (0.20 - 2.58) | 0.510 |
|  Q 0.5-0.75 (0.02-1 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (1-3 mmHg ·min) | 0.58 (0.33 - 1.04) | 0.016 | 0.57 (0.32 - 1.02) | 0.013 |
|  Q 0.9-1.0 (3-17 mmHg ·min) | 0.63 (0.34 - 1.16) | 0.052 | 0.61 (0.33 - 1.13) | 0.038 |
| MAP < 80 mmHg (N = 761, 99.2%; sign. p < 0.008) |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 0.68 (0.43 - 1.06) | 0.023 | 0.87 (0.53 - 1.43) | 0.464 |
|  Q 0-0.25 (0-0.05 mmHg ·min) | 1.08 (0.38 - 3.06) | 0.849 | 1.08 (0.37 - 3.16) | 0.854 |
|  Q 0.25-0.5 (0.05-2 mmHg ·min) | 0.92 (0.57 - 1.49) | 0.654 | 0.91 (0.56 - 1.47) | 0.607 |
|  Q 0.5-0.75 (2-7 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (7-12 mmHg ·min) | 0.63 (0.35 - 1.11) | 0.032 | 0.62 (0.35 - 1.11) | 0.030 |
|  Q 0.9-1.0 (12-27 mmHg ·min) | 0.69 (0.36 - 1.32) | 0.133 | 0.68 (0.36 - 1.30) | 0.116 |
| MAP > 90 mmHg (N= 580, CI 99.0%; sign. p < 0.010) |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 0.80 (0.53 - 1.20) | 0.157 | 0.91 (0.60 - 1.39) | 0.597 |
|  Q 0-0.5 (0-0.11 mmHg ·min) | 0.95 (0.50 - 1.82) | 0.861 | 0.93 (0.49 - 1.77) | 0.779 |
|  Q 0.5-0.75 (0.11-2 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (2-6 mmHg ·min) | 1.02 (0.58 - 1.80) | 0.925 | 1.02 (0.58 - 1.80) | 0.930 |
|  Q 0.9-1.0 (6-47 mmHg ·min) | 1.01 (0.56 - 1.84) | 0.960 | 1.03 (0.57 - 1.88) | 0.904 |
| MAP > 100 mmHg (N = 319, CI 98.8%; sign. p < 0.013)  |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 1.05 (0.57 - 1.95) | 0.853 | 1.16 (0.62 - 2.18) | 0.556 |
|  Q 0-0.75 (0-0.08 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (0.08-1 mmHg ·min) | 1.26 (0.60 - 2.66) | 0.440 | 1.27 (0.60 - 2.68) | 0.441 |
|  Q 0.9-1.0 (1-38 mmHg ·min) | 1.23 (0.58 - 2.60) | 0.510 | 1.26 (0.59 - 2.68) | 0.459 |
| MAP < 70% (N = 446, CI 99.0%; sign p < 0.010)  |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 1.32 (0.86 - 2.03) | 0.093 | 0.95 (0.59 - 1.54) | 0.802 |
|  Q 0-0.5 (0-0.13 mmHg ·min) | 0.58 (0.25 - 1.38) | 0.104 | 0.58 (0.24 - 1.40) | 0.114 |
|  Q 0.5 -0.75 (0.13-3 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75 -0.9 (3-8 mmHg ·min) | 0.83 (0.44 - 1.57) | 0.471 | 0.86 (0.45 - 1.61) | 0.535 |
|  Q 0.9-1.0 (8-38 mmHg ·min) | 0.80 (0.38 - 1.68) | 0.440 | 0.80 (0.38 - 1.70) | 0.459 |
| MAP < 60% (N =199, CI 98.8%; sign. p < 0.013)  |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 0.10 (0.01 - 1.45) | 0.031 | 0.08 (0.00 - 1.60) | 0.034 |
|  Q 0-0.75 (0-0.01 mmHg ·min) | ref = 1 |   | ref = 1 |  |
|  Q 0.75-0.9 (0.01-1 mmHg ·min) | 0.10 (0.01 - 1.56) | 0.037 | 0.11 (0.00 - 2.31) | 0.068 |
|  Q 0.9-1.0 (1-22 mmHg ·min) | 0.05 (0.00 - 0.79) | 0.007\* | 0.05 (0.00 - 1.15) | 0.017 |
| MAP < 50% (N= 43, CI 97.5%; sign. p < 0.025)  |   |   |   |  |
|  Q 0 (0 mmHg ·min) | 1.75 (0.80 - 3.82) | 0.106 | 1.41 (0.63 - 3.14) | 0.346 |
|  Q 0-1 (0-0.633) mmHg ·min) | ref = 1 |   | ref = 1 |   |

*CI: confidence interval. ETCO2: end-tidal carbon dioxide. MAP: mean arterial blood pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile.*

*\* significant difference*

† *Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals are reported accordingly. For example: when four categories were made within a threshold, a p-value of < 0.0125 was considered as statistical significant after a Bonferroni correction (0.05/4) with a corresponding confidence interval of 98.8%.*

*Poor neurological outcome was defined as a Glasgow Outcome Scale of 1-3.*