**Supplemental Digital Content 6**

**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 Results for interaction in the association between time-weighted average area-under-the curve thresholds for ETCO2 and MAP and neurological outcome at discharge**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Threshold and categories †** | **Interaction**  **Treatment modality** | | **Interaction**  **Preoperative WFNS** | | **Interaction**  **Timing of intervention** | |
| N = number of patients with TWA-AUC > 0  CI and sign. level for p-value are reported per threshold † | Adjusted RR (CI) *‡* | p-value | Adjusted RR (CI) *‡* | p-value | Adjusted RR (CI) *‡* | p-value |
| ETCO2 < 30 mmHg (N = 405; CI 98.8%; sign. p < 0.013) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 0.87 (0.51 - 1.49) | 0.526 | 1.11 (0.67 - 1.87) | 0.613 | 1.09 (0.59 - 2.00) | 0.737 |
| Q 0-0.75 (0-0.8 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (0.8-6.5 mmHg ·min) | 0.82 (0.42 - 1.59) | 0.454 | 1.19 (0.61 - 2.29) | 0.530 | 1.56 (0.74 - 3.29) | 0.137 |
| Q 0.9-1.0 (6.5-57.2 mmHg ·min) | 0.91 (0.42 - 1.97) | 0.767 | 1.75 (0.87 - 3.54) | 0.046 | 0.95 (0.42 - 2.15) | 0.884 |
| ETCO2 < 35 mmHg (N = 1022, CI 99.3%; sign. p < 0.007) |  |  |  |  |  |  |
| Q 0 ( 0 mmHg ·min) | 1.94 (0.54 - 6.96) | 0.166 | 0.79 (0.39 - 1.60) | 0.382 | 0.70 (0.27 - 1.80) | 0.318 |
| Q 0-0.1 (0-1.2 mmHg ·min) | 1.36 (0.47 - 3.92) | 0.441 | 1.52 (0.58 - 3.99) | 0.245 | 0.47 (0.14 - 1.56) | 0.090 |
| Q 0.1-0.25 (1.2-9.8 mmHg ·min) | 1.36 (0.71 - 2.60) | 0.200 | 1.10 (0.61 - 1.98) | 0.688 | 0.55 (0.24 - 1.24) | 0.046 |
| Q 0.25-0.5 (9.8-23.8 mmHg ·min) | 1.05 (0.61 - 1.79) | 0.830 | 1.36 (0.81 - 2.27) | 0.111 | 0.71 (0.39 - 1.30) | 0.132 |
| Q 0.5-0.75 (23.8-39.5 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (39.5-52.6 mmHg ·min) | 1.25 (0.66 - 2.37) | 0.361 | 1.07 (0.58 - 1.95) | 0.789 | 1.08 (0.55 - 2.13) | 0.762 |
| Q 0.9-1.0 (52.6-107.1 mmHg ·min) | 1.38 (0.65 - 2.94) | 0.257 | 2.00 (0.99 - 4.03) | 0.008 | 0.61 (0.25 - 1.48) | 0.132 |
| ETCO2 < 40 mmHg (N = 1072, CI 99.3%; sign. p < 0.007) |  |  |  |  |  |  |
| Q 0 ( 0 mmHg ·min) | 1.21 (0.27 - 5.49) | 0.751 | 0.69 (0.17 - 2.76) | 0.476 | 0.66 (0.08 - 5.26) | 0.602 |
| Q 0-0.1 (0-41.9 mmHg ·min) | 3.17 (1.17 - 8.59) | 0.002\* | 0.89 (0.45 - 1.78) | 0.665 | 0.61 (0.24 - 1.53) | 0.147 |
| Q 0.1-0.25 (41.9-56.5 mmHg ·min) | 1.09 (0.60 - 1.99) | 0.717 | 1.26 (0.72 - 2.21) | 0.278 | 0.78 (0.36 - 1.67) | 0.388 |
| Q 0.25-0.5 (56.5-71.8 mmHg ·min) | 1.06 (0.62 - 1.80) | 0.796 | 1.19 (0.72 - 1.98) | 0.361 | 0.75 (0.41 - 1.38) | 0.205 |
| Q 0.5-0.75 (71.8-88.0 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (88.0-101.3 mmHg ·min) | 1.30 (0.67 - 2.52) | 0.282 | 0.97 (0.52 - 1.80) | 0.901 | 1.11 (0.55 - 2.25) | 0.700 |
| Q 0.9-1.0 (101.3-156.3 mmHg ·min) | 1.38 (0.65 - 2.95) | 0.255 | 1.90 (0.95 - 3.82) | 0.013 | 0.70 (0.29 - 1.68) | 0.278 |
| ETCO2 < 45 mmHg (N= 1074, CI 99.3%; sign. p < 0.007) |  |  |  |  |  |  |
| Q 0 ( 0 mmHg ·min) | 1.08 (0.22 - 5.26) | 0.900 | 0.67 (0.10 - 4.53) | 0.590 | 0.73 (0.09 - 5.94) | 0.697 |
| Q 0-0.1 (0-90.3 mmHg ·min) | 2.91 (1.15 - 7.33) | 0.002\* | 0.93 (0.47 - 1.81) | 0.771 | 0.63 (0.25 - 1.60) | 0.181 |
| Q 0.1-0.25 (90.3-105.7 mmHg ·min) | 0.93 (0.50 - 1.75) | 0.784 | 1.21 (0.68 - 2.15) | 0.376 | 0.92 (0.44 - 1.94) | 0.783 |
| Q 0.25-0.5 (105.7-121.2 mmHg ·min) | 0.96 (0.56 - 1.63) | 0.834 | 1.27 (0.76 - 2.13) | 0.220 | 0.85 (0.45 - 1.59) | 0.485 |
| Q 0.5-0.75 (121.2-137.5 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (137.5-151.1 mmHg ·min) | 1.21 (0.63 - 2.32) | 0.452 | 0.99 (0.53 - 1.84) | 0.972 | 1.14 (0.56 - 2.31) | 0.636 |
| Q 0.9-1.0 (151.1-206.2 mmHg ·min) | 1.27 (0.58 - 2.76) | 0.423 | 1.89 (0.93 - 3.84) | 0.016 | 0.76 (0.31 - 1.84) | 0.410 |
| MAP < 60 mmHg (N = 166, CI 98.3%; sign. p < 0.017) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 2.36 (0.57 - 9.69) | 0.146 | 1.61 (0.82 - 3.17) | 0.091 | 0.73 (0.34 - 1.57) | 0.330 |
| Q 0-0.9 (0-0.11 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.9-.1.0 (0.11-7 mmHg ·min) | 2.58 (0.58 - 11.43) | 0.128 | 1.69 (0.71 - 4.01) | 0.149 | 0.65 (0.22 - 1.91) | 0.349 |
| MAP < 70 mmHg (N = 503, CI 99.0%; sign. p< 0.010) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 0.86 (0.56 - 1.32) | 0.379 | 1.03 (0.68 - 1.55) | 0.885 | 1.02 (0.60 - 1.72) | 0.927 |
| Q 0-0.5 (0-0.02 mmHg ·min) | 1.26 (0.06 - 25.09) | 0.855 | 1.64 (0.36 - 7.50) | 0.412 | 0.53 (0.09 - 3.16) | 0.369 |
| Q 0.5-0.75 (0.02-1 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (1-3 mmHg ·min) | 0.62 (0.33 - 1.18) | 0.056 | 1.04 (0.56 - 1.94) | 0.880 | 1.28 (0.59 - 2.79) | 0.423 |
| Q 0.9-1.0 (3-17 mmHg ·min) | 0.85 (0.42 - 1.73) | 0.573 | 0.88 (0.44 - 1.74) | 0.633 | 1.23 (0.52 - 2.95) | 0.547 |
| MAP < 80 mmHg (N = 761, 99.2%; sign. p < 0.008) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 1.21 (0.72 - 2.03) | 0.343 | 1.02 (0.62 - 1.68) | 0.925 | 0.98 (0.52 - 1.84) | 0.924 |
| Q 0-0.25 (0-0.05 mmHg ·min) | 0.64 (0.10 - 4.26) | 0.543 | 0.95 (0.34 - 2.65) | 0.897 | 1.25 (0.39 - 4.03) | 0.625 |
| Q 0.25-0.5 (0.05-2 mmHg ·min) | 1.38 (0.84 - 2.26) | 0.087 | 1.23 (0.76 - 2.00) | 0.264 | 0.95 (0.50 - 1.79) | 0.827 |
| Q 0.5-0.75 (2-7 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (7-12 mmHg ·min) | 0.98 (0.53 - 1.80) | 0.931 | 1.39 (0.74 - 2.60) | 0.171 | 1.26 (0.58 - 2.76) | 0.437 |
| Q 0.9-1.0 (12-27 mmHg ·min) | 1.14 (0.53 - 2.45) | 0.657 | 0.89 (0.43 - 1.83) | 0.673 | 1.26 (0.49 - 3.21) | 0.531 |
| MAP > 90 mmHg (N= 580, CI 99.0%; sign. p < 0.010) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 1.04 (0.66 - 1.64) | 0.845 | 0.96 (0.63 - 1.48) | 0.836 | 1.17 (0.66 - 2.06) | 0.497 |
| Q 0-0.5 (0-0.11 mmHg ·min) | 1.37 (0.66 - 2.88) | 0.272 | 0.79 (0.39 - 1.61) | 0.398 | 0.77 (0.32 - 1.82) | 0.435 |
| Q 0.5-0.75 (0.11-2 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (2-6 mmHg ·min) | 1.69 (0.93 - 3.08) | 0.024 | 0.92 (0.51 - 1.68) | 0.746 | 0.80 (0.40 - 1.61) | 0.419 |
| Q 0.9-1.0 (6-47 mmHg ·min) | 1.08 (0.57 - 2.04) | 0.770 | 0.92 (0.48 - 1.77) | 0.757 | 1.04 (0.50 - 2.16) | 0.895 |
| MAP > 100 mmHg (N = 319, CI 98.8%; sign. p < 0.013) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 0.83 (0.35 - 1.96) | 0.597 | 1.19 (0.59 - 2.38) | 0.553 | 1.58 (0.62 - 3.99) | 0.221 |
| Q 0-0.75 (0-0.08 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (0.08-1 mmHg ·min) | 1.35 (0.49 - 3.77) | 0.469 | 1.06 (0.47 - 2.42) | 0.861 | 1.50 (0.52 - 4.32) | 0.344 |
| Q 0.9-1.0 (1-38 mmHg ·min) | 1.17 (0.44 - 3.13) | 0.695 | 1.16 (0.49 - 2.75) | 0.685 | 1.42 (0.50 - 4.03) | 0.408 |
| MAP < 70% (CI 99.0%; sign p < 0.010) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 1.14 (0.62-2.08) | 0.587 | 0.85 (0.48-1.53) | 0.496 | 0.84 (0.42-1.66) | 0.513 |
| Q 0-0.5 (0-0.13 mmHg ·min) | 1.23 (0.36-4.23) | 0.678 | 1.17 (0.28-4.85) | 0.791 | 0.83 (0.22-3.12) | 0.726 |
| Q 0.5 -0.75 (0.13-3 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75 -0.9 (3-8 mmHg ·min) | 0.84 (0.37-1.93) | 0.609 | 0.83 (0.37-1.84) | 0.559 | 0.83 (0.37-1.82) | 0.543 |
| Q 0.9-1.0 (8-38 mmHg ·min) | 1.28 (0.45-3.64) | 0.553 | 0.74 (0.23-2.38) | 0.520 | 0.83 (0.28-2.49) | 0.678 |
| MAP < 60% (CI 98.8%; sign. p < 0.013) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 0.55 (0.03-11.22) | 0.637 | 2.20 (0.32-15.28) | 0.313 | 1.25 (0.12-13.18) | 0.823 |
| Q 0-0.75 (0-0.01 mmHg ·min) | ref = 1 |  | ref = 1 |  | ref = 1 |  |
| Q 0.75-0.9 (0.01-1 mmHg ·min) | 0.48 (0.02-10.12) | 0.556 | 1.85 (0.26-13.11) | 0.442 | 1.21 (0.11-13.72) | 0.853 |
| Q 0.9-1.0 (1-22 mmHg ·min) | 0.74 (0.03-17.80) | 0.822 | 1.89 (0.16-22.20) | 0.530 | 1.03 (0.08-13.56) | 0.980 |
| MAP < 50% (CI 97.5%; sign. p < 0.025) |  |  |  |  |  |  |
| Q 0 (0 mmHg ·min) | 0.51 (0.09-2.86) | 0.391 | 0.80 (0.22-2.93) | 0.710 | 1.79 (0.62-5.15) | 0.216 |
| Q 0-1 (0-0.633) mmHg ·min) | ref = 1 |  | 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. TWA-AUC: time-weighted average area-under-the-curve. WFNS: World Federation of Neurological Surgeons Grading System Score*

*\* 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%.*

*‡ The models were adjusted for age, gender, history of myocardial infarction, cerebrovascular disease, diabetes mellitus, hypertension, vascular disorders (central and peripheral), (history of) smoking, World Federation of Neurological Surgeons Grading System Score on admission, intervention modality (clipping or coiling), day of intervention, number of times receiving general anesthesia prior to and after the intervention, cerebral spinal fluid drainage, postoperative neurological decline, re-bleed, edema, cerebral ischemia, hydrocephalus, anemia, extracranial complications, preoperative MAP, amount of ephedrine, phenylephrine and noradrenaline per hour, preoperative oxygenation level and year of procedure. Additionally, the results for the ETCO2 thresholds were adjusted for the mean MAP per case, whereas the results for the MAP thresholds were adjusted for the mean ETCO2 per case.*

*Poor neurological outcome was defined as a Glasgow Outcome Scale of 1-3. Treatment modality was defined as clipping or coiling. Preoperative WFNS was dichotomized into “4,5” versus “1,2,3”. Timing of intervention was dichotomized into “within 2 days after the ictus” and “after two days after the ictus”.*

**Table 2 Results for interaction in the association between mean MAP, mean ETCO2, any ETCO2 < 30 mmHg and any MAP < 60 mmHg and neurological outcome at discharge**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Threshold and categories** † | **Interaction**  **Treatment modality** | | **Interaction**  **Preoperative WFNS** | | **Interaction**  **Timing of intervention** | |
| N = number of patients with TWA-AUC or Mean > 0 | Adjusted RR (CI ) *‡* | p-value | Adjusted RR (CI) *‡* | p-value | Adjusted RR (CI) *‡* | p-value |
| CI and sign. level for p-value are reported per threshold † |
| Mean MAP (N = 974, 99.2% CI; sign. p < 0.008) |  |  |  |  |  |  |
| Q 0-0.1 (53-67.8 mmHg) | 0.96 (0.43-2.14) | 0.898 | 0.75 (0.35-1.61) | 0.321 | 1.34 (0.54-3.34) | 0.402 |
| Q 0.1-0.25 (67.8-73.2 mmHg) | 0.77 (0.43-1.38) | 0.238 | 1.05 (0.57-1.91) | 0.852 | 1.29 (0.61-2.69) | 0.375 |
| Q 0.25-0.5 (73.2-80.6 mmHg) | 0.92 (0.55-1.54) | 0.679 | 0.72 (0.44-1.18) | 0.080 | 1.23 (0.64-2.37) | 0.405 |
| Q 0.5-0.75 (80.6-88.3 mmHg) | ref = 1 |  | ref =1 |  | ref = 1 |  |
| Q 0.75-0.9 (88.3-95.5 mmHg) | 1.03 (0.60-1.76) | 0.907 | 0.79 (0.46-1.36) | 0.257 | 1.13 (0.60-2.14) | 0.623 |
| Q 0.9-1.0 (95.5-138 mmHg) | 0.94 (0.47-1.97) | 0.812 | 0.81 (0.40-1.66) | 0.452 | 1.12 (0.51-2.43) | 0.720 |
| Mean EtCO2 (N = 1096, 99.2% CI, sign. p < 0.008) |  |  |  |  |  |  |
| Q 0-0.1 (32-39.6mmHg) | 1.20 (0.58-2.51) | 0.519 | 1.67 (0.86-3.23) | 0.040 | 0.91 (0.39-2.12) | 0.776 |
| Q 0.1-0.25 (39.6-41.3mmHg) | 1.04 (0.57-1.92) | 0.860 | 0.79 (0.45-1.39) | 0.276 | 1.68 (0.89-3.18) | 0.031 |
| Q 0.25-0.5 (41.3-43.5mmHg) | 0.97 (0.58-1.62) | 0.869 | 0.87 (0.53-1.43) | 0.463 | 1.13 (0.61-2.10) | 0.607 |
| Q 0.5-0.75 (43.5-45.6mmHg) | ref = 1 |  | ref =1 |  | ref = 1 |  |
| Q 0.75-0.9 (45.6-47.3mmHg) | 1.14 (0.64-2.04) | 0.552 | 1.11 (0.64-1.94) | 0.630 | 0.96 (0.44-2.09) | 0.888 |
| Q 0.9-1.0 (47.3-56 mmHg) | 1.42 (0.66-3.06) | 0.234 | 0.71 (0.41-1.24) | 0.110 | 0.83 (0.37-1.85) | 0.549 |
| Any ETCO2 <30 mmHg (N = 405, 95% CI, sign. p < 0.05) | 0.98 (0.73-1.30) | 0.877 | 1.10 (0.84-1.43) | 0.497 | 1.04 (0.75-1.45) | 0.805 |
| Any MAP < 60 mmHg (N = 166, 95% CI, sign. p < 0.05) | 0.85 (0.56-1.27) | 0.428 | 0.84 (0.59-1.20) | 0.347 | 1.09 (0.70-1.71) | 0.718 |

*CI: confidence interval. ETCO2: end-tidal carbon dioxide. MAP: mean arterial blood pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile. WFNS: World Federation of Neurological Surgeons Grading System Score*

*\* 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%.*

*‡ The models were adjusted for age, gender, history of myocardial infarction, cerebrovascular disease, diabetes mellitus, hypertension, vascular disorders (central and peripheral), (history of) smoking, World Federation of Neurological Surgeons Grading System Score on admission, intervention modality (clipping or coiling), day of intervention, number of times receiving general anesthesia prior to and after the intervention, cerebral spinal fluid drainage, postoperative neurological decline, re-bleed, edema, cerebral ischemia, hydrocephalus, anemia, extracranial complications, preoperative MAP, amount of ephedrine, phenylephrine and noradrenaline per hour, preoperative oxygenation level and year of procedure. Additionally, the results for the ETCO2 thresholds were adjusted for the mean MAP per case, whereas the results for the MAP thresholds were adjusted for the mean ETCO2 per case.*

*Poor neurological outcome was defined as a Glasgow Outcome Scale of 1-3. Treatment modality was defined as clipping or coiling. Preoperative WFNS was dichotomized into “4,5” versus “1,2,3”. Timing of intervention was dichotomized into “within 2 days after the ictus” and “after two days after the ictus”.*