

## ANESTHESIOLOGY

# Blood Pressure and End-tidal Carbon Dioxide Ranges during Aneurysm Occlusion and Neurologic Outcome after an Aneurysmal Subarachnoid Hemorrhage

Annemarie Akkermans, M.D., Judith A. van Waes, M.D., Ph.D., Linda M. Peelen, Ph.D., Gabriel J. Rinkel, M.D., F.R.C.P.(E.), Wilton A. van Klei, M.D., Ph.D.

*ANESTHESIOLOGY* 2019; 130:92–105

Despite considerable treatment improvements over the past decades, case fatality and disability rates for patients with aneurysmal subarachnoid hemorrhage remain high.<sup>1–3</sup> After aneurysmal subarachnoid hemorrhage, the cerebral autoregulation is disrupted and cerebral blood flow may become blood pressure dependent. Therefore, in patients undergoing general anesthesia for an intervention to obliterate the aneurysm, maintaining adequate blood pressure is considered important to avoid both hypertension-related rebleeding, as well as hypotension-related cerebral ischemia.<sup>1,4</sup> However, because only a few relatively small studies have been performed in this specific population,<sup>5–7</sup> solid recommendations on periprocedural blood pressure targets are lacking.<sup>2</sup>

In addition, arterial carbon dioxide tension ( $P_{aCO_2}$ ) reactivity seems preserved, or even increased, in aneurysmal subarachnoid hemorrhage patients; therefore, hypocapnia can aggravate secondary ischemia through cerebral vasoconstriction.<sup>8</sup> Hypocapnia has been shown to be associated with a poor neurologic outcome in patients with traumatic brain injury, with ischemic stroke, or after a cardiac arrest.<sup>9–11</sup> While evidence specifically for aneurysmal subarachnoid hemorrhage patients is lacking, there is evidence supporting the benefit of hypercapnia for postoperative outcomes in the general surgery population.<sup>12–14</sup> Although  $P_{aCO_2}$  not monitored continuously, it is well reflected in the end-tidal carbon dioxide ( $ETCO_2$ ), which is routinely monitored during anesthesia.

All together, there is insufficient evidence to determine optimal target ranges for both  $ETCO_2$  and mean arterial

## ABSTRACT

**Background:** Hypocapnia, hypotension, and hypertension during aneurysm occlusion in patients with an aneurysmal subarachnoid hemorrhage may lead to a poor prognosis, but evidence for end-tidal carbon dioxide ( $ETCO_2$ ) and mean arterial pressure (MAP) targets is lacking. Within the ranges of standardized treatment, the authors aimed to study the association between hypocapnia ( $P_{aCO_2} < 35$  mmHg), hypotension (MAP  $< 80$  mmHg), and hypertension (MAP  $> 100$  mmHg) during general anesthesia for aneurysm occlusion and neurologic outcome.

**Methods:** This retrospective observational study included patients who underwent early aneurysm occlusion after an aneurysmal subarachnoid hemorrhage under general anesthesia.  $ETCO_2$  and MAP were summarized per patient as the mean and time-weighted average area under the curve for various absolute ( $ETCO_2 < 30, < 35, < 40, < 45$  mmHg; and MAP  $< 60, < 70, < 80, > 90, > 100$  mmHg) and relative thresholds (MAP  $< 70\%, < 60\%, < 50\%$ ). Clinical outcome was assessed with the Glasgow Outcome Scale at discharge and at three months, as primary and secondary outcome measure, respectively.

**Results:** Endovascular coiling was performed in 578 patients, and 521 underwent neurosurgical clipping. Of these 1,099 patients, 447 (41%) had a poor neurologic outcome at discharge. None of the  $ETCO_2$  and MAP ranges found within the current clinical setting were associated with a poor neurologic outcome at discharge, with an adjusted risk ratio for any  $ETCO_2$  value less than 30 mmHg of 0.95 (95% CI, 0.81 to 1.10;  $P < 0.496$ ) and an adjusted risk ratio for any MAP less than 60 mmHg of 0.94 (95% CI, 0.78 to 1.14;  $P < 0.530$ ). These results were not influenced by preoperative neurologic condition, treatment modality and timing of the intervention. Comparable results were obtained for neurologic outcome at three months.

**Conclusions:** Within a standardized intraoperative treatment strategy in accordance with current clinical consensus, hypocapnia, hypotension, and hypertension during aneurysm occlusion were not found to be associated with a poor neurologic outcome at discharge in patients with an aneurysmal subarachnoid hemorrhage.

(ANESTHESIOLOGY 2019; 130:92–105)

## EDITOR'S PERSPECTIVE

## What We Already Know about This Topic

- It remains unknown what end-tidal carbon dioxide and mean arterial pressure are optimal for surgical management of patients with an aneurysmal subarachnoid hemorrhage

## What This Article Tells Us That Is New

- The investigators retrospectively evaluated 1,099 patients who had endovascular coiling or surgical clipping for subarachnoid hemorrhages
- There were no clinically important or statistical significant associations between either end-tidal carbon dioxide or mean arterial pressure thresholds and Glasgow Outcome Scale at discharge or three months
- Other prognostic factors are more important than carbon dioxide and blood pressure, at least within the observed clinical ranges

pressure (MAP) during anesthesia for interventions to treat cerebral aneurysms after aneurysmal subarachnoid hemorrhage. Therefore, this study sets out to explore the association between several intraoperative ETco<sub>2</sub> and MAP thresholds and a poor neurologic outcome in a large cohort of aneurysmal subarachnoid hemorrhage patients who were treated according to a standardized institutional strategy based on current clinical consensus. The results may guide clinicians in setting periprocedural target ranges in the future. On the basis of the aforementioned literature, we hypothesized that prolonged (greater than 10 min) intraoperative hypocapnia (ETco<sub>2</sub> < 35 mmHg), hypotension (MAP < 80 mmHg), and hypertension (MAP > 100 mmHg) are associated with a poor neurologic outcome in aneurysmal subarachnoid hemorrhage patients receiving general anesthesia for interventions to treat cerebral aneurysms.

## Material and Methods

This study was conducted in adherence to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational research.<sup>15</sup> The local medical ethics committee approved the study protocol, and the need for informed consent was waived (University Medical Center Utrecht Medical Research Ethics Committee 16 to 194/C).

## Patients

This retrospective observational study included adult patients who received general anesthesia for neurosurgical clipping or endovascular coiling of a ruptured intracranial aneurysm at the University Medical Center Utrecht in the Netherlands between January 2003 and December 2015. Patients who were treated within 2 weeks after the ictus were eligible for inclusion. Reinterventions in patients who had more than one episode of aneurysmal subarachnoid hemorrhage were included as a new patient if the time between these episodes was more than 1 yr. Patients were excluded if they underwent bypass surgery for a giant aneurysm. Furthermore, patients were excluded if fewer than a total of 20 valid ETco<sub>2</sub> and MAP measurements were available, or when no MAP and ETco<sub>2</sub> data were recorded for at least 10 consecutive minutes during the procedure.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site ([www.anesthesiology.org](http://www.anesthesiology.org)).

Submitted for publication May 31, 2018. Accepted for publication September 18, 2018. From the Department of Anesthesiology (A.A., J.A.v.W., L.M.P., W.A.v.K.); the Department of Epidemiology, Julius Center for Health Sciences and Primary Care (L.M.P.); and the Department of Neurology and Neurosurgery, Brain Centre Rudolf Magnus (G.J.R.), University Medical Center Utrecht, Utrecht University, The Netherlands.

When no ETco<sub>2</sub> data were recorded, patients could still be included for blood pressure analyses and *vice versa*. Patients without a known baseline blood pressure were excluded from analyses for relative blood pressure thresholds only.

Patients were treated according to a local standardized protocol,<sup>5</sup> and the preferred neurosurgical treatment modality was chosen on a multidisciplinary level and irrespective of the conduct of this study. Management of blood pressure and ETco<sub>2</sub> were left to the judgment of the attending anesthesiologist. The protocol prescribed to maintain ETco<sub>2</sub> between 35 and 45 mmHg and to keep the systolic blood pressure (SBP) less than 180 mmHg before treatment and less than 220 mmHg after securing the aneurysm, while maintaining a MAP greater than 80 mmHg.

## Outcomes

The primary outcome was the neurologic outcome at discharge, using the Glasgow Outcome Scale<sup>16</sup> (see table 1, Supplemental Digital Content 1, <http://links.lww.com/ALN/B791>, listing neurologic scoring systems). The Glasgow Outcome Scale at three months was used as a secondary outcome. We defined a good outcome as a Glasgow Outcome Scale score of 4 or 5, and a poor outcome as a Glasgow Outcome Scale score 1 to 3.

## MAP and ETco<sub>2</sub>

To analyze the effect of ETco<sub>2</sub> and blood pressure on a poor neurologic outcome, we determined the mean ETco<sub>2</sub> and the mean MAP for each patient. However, as those summary measures do not sufficiently take normal intraoperative variability into account,<sup>17</sup> we further used a time-weighted average area under the curve for several absolute and relative thresholds. The time-weighted average area under the curve represents the time spent under or above a certain threshold, adjusted for the total measurement time. For ETco<sub>2</sub>, we defined the following absolute thresholds: less than 30 mmHg, less than 35 mmHg, less than 40 mmHg, and less than 45 mmHg, based on clinical relevance. For blood pressure, the following absolute and relative thresholds were defined: MAP < 60 mmHg, MAP < 70 mmHg, MAP < 80 mmHg, MAP > 90 mmHg, MAP > 100 mmHg and MAP < 70%, MAP < 60%, and MAP < 50% of the baseline MAP, based on reported thresholds in the literature.<sup>18,19</sup>

To define the baseline MAP, we used the mean of all preinduction MAPs per patient obtained at the operation room. Previous research in the general surgery population has shown that preinduction blood pressure can be used as a baseline for research purposes.<sup>20</sup>

## Data Collection

Data on patient characteristics, comorbidities, and chronic medication use were collected from electronic medical files. Data on preoperative neurologic condition, neurologic

complications, and postoperative neurologic outcomes were obtained from the local hospital aneurysmal subarachnoid hemorrhage registration database that contains data from admission until three months after the ictus.

Intraoperative data were extracted from the electronic anesthesia record keeping system (Anstat; Carepoint, Netherlands). Invasive blood pressure measurements,  $ETCO_2$  values and respiratory minute ventilation values were recorded as the median per minute; noninvasive blood pressure measurements were recorded every time a blood pressure was measured (*i.e.*, at 1- to 3-min intervals). Respiratory minute ventilation was calculated as tidal volume times respiratory rate. To avoid influences from induction and emergence from anesthesia on  $ETCO_2$  and MAP values, extraction of intraoperative data started 10 min after surgical incision and stopped 10 min before the end of the procedure. The duration of surgery was defined as the time between surgical incision and end of the procedure. Data artifacts were excluded using criteria based on prior research (see table 1, Supplemental Digital Content 2, <http://links.lww.com/ALN/B792>, presenting the artifact definitions used for intraoperatively measured variables).<sup>21,22</sup>

No statistical power calculation was conducted before the start of the study. The sample size was based on the available data.

### Missing Data

As complete case analyses are known to lead to biased effect estimates, missing values were handled using multiple imputation.<sup>23</sup> We used the Multivariate Imputation by Chained Equations package in R, creating 30 imputation sets.<sup>24</sup> Analyses were conducted in each of these datasets; subsequently estimates were pooled using Rubin's rule.<sup>25,26</sup> Missing data for  $ETCO_2$ , MAP and respiratory minute ventilation were not imputed.

### Statistical Analyses

Baseline characteristics were compared between patients with a good outcome and poor outcome at discharge, and between patients presenting for endovascular coiling and neurosurgical clipping using a chi-square test, Fisher exact test, independent *t* test, or Mann-Whitney U test where appropriate. Continuous variables were checked for normality using the Kolmogorov-Smirnov test.

### Association between MAP and $ETCO_2$

Since changes in blood pressure are known to affect  $ETCO_2$  concentrations by influencing the  $ETCO_2$ - $Paco_2$  gradient,<sup>27</sup> we first estimated the effect of changes in MAP on changes in  $ETCO_2$ . First, in each patient, the median of all obtained  $ETCO_2$ , MAP, and respiratory minute

ventilation values was calculated. Next, we determined the difference ( $\Delta$ ) between the median and each other value of  $ETCO_2$ , MAP, and respiratory minute ventilation.  $\Delta$ MAP and  $\Delta$ respiratory minute ventilation were paired with  $\Delta$  $ETCO_2$  values that were obtained one minute later, to allow for a change in  $ETCO_2$  to occur. Next, because a nonlinear relationship between  $\Delta$  $ETCO_2$  and  $\Delta$ MAP was expected, a univariate linear quantile mixed regression model was made with 10 quantiles, using  $\Delta$  $ETCO_2$  as the dependent variable,  $\Delta$ MAP as the independent variable, and a random intercept per individual to take clustering within patients into account. Afterward, a multivariable analysis was used to adjust for changes in respiratory minute volume.

We considered that  $ETCO_2$  values should be adjusted for MAP values in the subsequent analyses if there was a significant and clinically relevant association between  $ETCO_2$  and MAP. In this, an effect estimate of 1.1 or higher for every 10 mmHg change in MAP was considered to be clinically relevant.

### Association between $ETCO_2$ and MAP and Neurologic Outcomes

In line with previous studies,<sup>10,28</sup> we first calculated a mean MAP and mean  $ETCO_2$  for each patient. Second, the area under the curve was calculated for each predefined threshold as mentioned in "Material and Methods, MAP and  $ETCO_2$ ", for both MAP and  $ETCO_2$ . This area under the curve was adjusted for the total measurement time, resulting in a time-weighted average area under the curve (see fig. 1, Supplemental Digital Content 3, <http://links.lww.com/ALN/B793>, showing how the area under the curve was calculated for several thresholds).

Next, univariable Poisson regression models were built using mean MAP, mean  $ETCO_2$ , time-weighted average area under the curve MAP, or time-weighted average area under the curve  $ETCO_2$  as the independent variable, respectively, and the dichotomized Glasgow Outcome Scale score at discharge as the dependent variable. We used Poisson regression analyses with robust standard errors to present effect estimates as risk ratios, because a poor neurologic outcome is relatively common and the rare disease assumption would not hold.<sup>29</sup> This means that an odds ratio, as found in a logistic regression analysis, would not approach the corresponding risk ratio, hampering the interpretation of our results for clinical practice. Because we expected a nonlinear relationship in these models based on previous research,<sup>30</sup> a restricted cubic spline function with three, four, and five knots was tested for the best fit, using Akaike information criterion.<sup>31</sup> A multivariable analysis was subsequently used to adjust for potential confounders. The variables shown in table 1 were considered a potential confounder and were checked for collinearity using a Pearson correlation matrix. Variables with a correlation

**Table 1.** Patient Characteristics for Good *versus* Poor Neurologic Outcome at Discharge and for Clipping *versus* Coiling

	GOS 4–5	GOS 1–3	P Value	Clipping	Coiling	P Value
n	652	447		521	578	
Age (median [IQR])	55 [46–64]	60 [49–70]	< 0.001*	55 [47–64]	58 [48–68]	0.006*
Sex (%), Male	186 (28.5)	119 (26.6)	0.532	140 (26.9)	165 (28.6)	0.581
BMI (median [IQR])	24.8 [22.4–28.2]	25.1 [22.0–28.5]	0.702	25.0 [22.3–28.1]	24.9 [22.2–28.5]	0.864
ASA (%)						
1	135 (20.7)	90 (19.9)	0.003*	128 (24.6)	97 (16.8)	0.006*
2	478 (73.3)	304 (68.2)		355 (68.1)	427 (73.9)	
3	39 (6.0)	52 (11.6)		38 (7.3)	53 (9.2)	
4	0 (0.0)	1 (0.2)		0 (0.0)	1 (0.2)	
Myocardial infarction (%)	26 (4.0)	33 (7.4)	0.021*	23 (4.4)	36 (6.2)	0.231
Congestive heart failure (%)	0 (0.0)	1 (0.2)	0.407	1 (0.2)	0 (0.0)	0.474
Cerebrovascular accident (%)	40 (6.1)	32 (7.2)	0.583	34 (6.5)	38 (6.6)	1.000
Diabetes mellitus (%)	26 (4.0)	23 (5.2)	0.444	20 (3.8)	29 (5.0)	0.424
Hypertension (%)	138 (21.2)	146 (32.4)	< 0.001*	117 (22.5)	167 (28.9)	0.018*
Vascular disease (%)	23 (3.5)	28 (6.3)	0.049*	24 (4.6)	27 (4.7)	1.000
Pulmonary disorder (%)	58 (8.9)	37 (8.3)	0.803	38 (7.3)	57 (9.9)	0.160
History of Smoking (%)						
Past	72 (11.0)	71 (15.9)	0.007*	73 (14.0)	70 (12.1)	0.029*
Current	355 (54.5)	204 (45.9)		243 (46.8)	316 (54.7)	
Use of anticoagulants on admission (%)	81 (12.4)	86 (19.2)	0.003*	74 (14.2)	93 (16.1)	0.432
Use of statins on admission (%)	71 (10.9)	73 (16.3)	0.011*	64 (12.5)	80 (13.8)	0.500
Use of antihypertensive drugs on admission (%)	141 (21.6)	144 (32.2)	< 0.001*	117 (22.5)	168 (29.1)	0.015*
WFNS on admission (%)						
1	393 (60.3)	113 (25.3)	< 0.001*	251 (48.4)	255 (44.1)	0.187
2	162 (24.9)	92 (20.6)		110 (21.1)	144 (24.9)	
3	32 (4.9)	38 (8.5)		31 (6.0)	39 (6.8)	
4	48 (7.4)	108 (24.2)		82 (15.6)	74 (12.8)	
5	17 (2.6)	96 (21.5)		47 (9.0)	66 (11.4)	
Type of intervention (%)						
Clipping	303 (46.5)	218 (48.8)	0.492			
Coiling	349 (53.5)	229 (51.2)				
Day of intervention (days, median [IQR])	2 [1–4]	1 [1–3]	< 0.001*	2 [1–4]	1 [1–3]	< 0.001*
Preintervention WFNS (%)						
1	421 (64.6)	121 (27.1)	< 0.001*	264 (50.7)	278 (48.1)	0.516
2	139 (21.3)	91 (20.4)		101 (19.4)	129 (22.3)	
3	28 (4.3)	36 (8.29)		28 (5.4)	36 (6.2)	
4	47 (7.2)	102 (22.6)		77 (14.8)	72 (12.5)	
5	17 (2.6)	97 (21.7)		51 (9.8)	63 (10.9)	
Preintervention intubation (%)	41 (6.3)	152 (34.0)	< 0.001*	87 (16.7)	106 (18.3)	0.526
Number of GA before intervention (%)						
1	43 (6.6)	93 (20.8)	< 0.001*	63 (12.1)	73 (12.6)	0.132
2	1 (0.2)	6 (1.3)		6 (1.2)	1 (0.2)	
Number of GA after intervention (%)						
1	31 (4.8)	81 (18.1)	< 0.001*	58 (11.1)	54 (9.3)	0.160
2	1 (0.2)	6 (1.3)		1 (0.2)	6 (1.0)	
3	0 (0.0)	4 (0.9)		3 (0.6)	1 (0.2)	
Cerebral spinal fluid drainage (%)	110 (16.9)	173 (38.9)	< 0.001*	181 (34.7)	102 (17.7)	< 0.001*
Coiling attempt prior to clipping (%)	16 (2.5)	15 (3.4)	0.483	31 (6.0)	0 (0.0)	< 0.001*
Preinduction Mean MAP (mmHg, median [IQR])	103 [94–114]	102 [91–113]	0.055	103 [94–115]	102 [92–112]	0.056
Mean MAP during intervention (mmHg, median [IQR])	80 [72–88]	81 [74–88]	0.021*	82 [75–89]	79 [71–87]	< 0.001*
Mean ET <sub>CO<sub>2</sub></sub> during intervention (mmHg, median [IQR])	43 [41–45]	44 [42–46]	< 0.001*	43 [41–45]	44 [42–46]	< 0.001*
Preinduction oxygenation (%), median [IQR])	97 [95–98]	97 [95–99]	0.926	97 [95–98]	97 [95–98]	0.005*
Duration of intervention (min, median [IQR])	129 [88–174]	122 [90–187]	0.110	174 [146–218]	91 [71–121]	< 0.001*
Duration of anesthesia (min, median [IQR])	177 [123–253]	185 [125–262]	0.133	256 [221–309]	126 [108–153]	< 0.001*
Ephedrine (mg/hour, median [IQR])†	0.0 [0.0–0.0]	0.00 [0.0–0.0]	0.751	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.077
Phenylephrine (µg/hour, median [IQR])†	0.0 [0.0–690.5]	0.0 [0.0–734.7]	0.539	0.0 [0.0–173.6]	66.7 [0.0–1026.7]	< 0.001*

(Continued)

**Table 1.** (Continued)

	GOS 4–5	GOS 1–3	P Value	Clipping	Coiling	P Value
Norepinephrine (µg/hour, median [IQR])†	0.0 [0.0–0.0]	0.0 [0.0–88.0]	< 0.001*	0.0 [0.0–88.0]	0.0 [0.0–0.0]	< 0.001*
Dopamine (%)	5 (0.8)	7 (1.6)	0.339	9 (1.7)	3 (0.5)	0.079
Dobutamine (%)	1 (0.2)	1(0.2)	1.000	1 (0.2)	1 (0.2)	1.000
Postintervention neurologic decline (%)	142 (21.8)	195 (43.6)	< 0.001*	189 (36.1)	148 (25.6)	< 0.001*
Complications‡						
Rebleed (%)	48 (7.4)	82 (18.3)	< 0.001*	65 (12.5)	65 (11.3)	0.591
Cerebral ischemia (%)	113 (17.3)	205 (45.9)	< 0.001*	164 (31.5)	154 (26.7)	0.089
Hydrocephalus (%)	123 (18.9)	228 (51.0)	< 0.001*	155 (29.8)	196 (33.9)	0.158
Cerebral edema (%)	23 (3.5)	54 (12.1)	< 0.001*	53 (10.2)	24 (4.2)	< 0.001*
Convulsion (%)	15 (2.3)	28 (6.3)	0.002*	23 (4.4)	20 (3.5)	0.510
Other intracranial complication (%)	70 (10.7)	93 (20.8)	< 0.001*	97 (18.6)	66 (11.4)	0.001*
Extracranial complication (%)	188 (28.8)	202 (45.2)	< 0.001*	167 (32.1)	223 (38.6)	0.028*
Hypernatremia (%)	47 (7.2)	131 (29.5)	< 0.001*	102 (19.6)	76 (13.2)	0.005*
Hyponatremia (%)	470 (72.1)	351 (78.5)	0.019*	392 (75.2)	429 (74.1)	0.750
Anemia (%)	95 (14.6)	170 (38.0)	< 0.001*	175 (33.6)	90 (15.6)	< 0.001*
Hypomagnesemia (%)	132 (20.3)	151 (33.8)	< 0.001*	151 (29.0)	132 (22.8)	0.024*
Hyperglycemia (%)	154 (23.6)	283 (63.3)	< 0.001*	219 (42.0)	218 (37.7)	0.162
Hypoglycemia (%)	61 (9.4)	134 (30.0)	< 0.001*	99 (19.0)	96 (16.6)	0.338
Length of stay (days, median [IQR])	18 [14–22]	21 [14–31]	< 0.001*	21 [16–27]	16 [14–21]	< 0.001*

\*Statistically significant at a level of significance of  $P < 0.05$ .

†Strongly skewed distribution.

‡ Hypoglycemia: glucose < 72 mg/dl (4mmol/l). Hyperglycemia: glucose 180 mg/dl (>10mM). Hyponatremia: sodium < 136 mEq/l (136 mM). Hypernatremia: sodium > 146 mEq/l (146 mM). Hypomagnesemia: magnesium < 1.7 mg/dl (0.70 mM). Anemia: hemoglobin < 9.7 g/dl (6 mM).

ASA, American Society of Anesthesiologists; BMI, body mass index; ETco<sub>2</sub>, end-tidal carbon dioxide concentration; GA, general anesthesia; GOS, Glasgow Outcome Scale (GOS 4, 5 [good neurologic outcome]; GOS 1, 2, 3 [poor neurologic outcome]); IQR, interquartile range; MAP, mean arterial blood pressure; WFNS, World Federation of Neurologic Surgeons Grading System for aneurysmal subarachnoid hemorrhage (1 = optimal score, 5 = worst score).

of less than 0.6 were included in the model. In case of multicollinearity, the clinically most relevant variable was included. In addition, year of procedure was included as a potential confounder to account for possible changes in clinical practice over time.

To enhance clinical interpretation, the Poisson regression analyses were repeated using categorized versions of the independent variables, where categorization was based on distribution of the data and inspection of the spline plots. We used the following quantiles: 0, 0.1, 0.25, 0.5, 0.75, 0.9, and 1.0, with the 0.5 to 0.75 quantile as the reference category.

Finally, we explored the effect of extreme hypocapnia and hypotension further by repeating the analyses using “having at least one ETco<sub>2</sub> value less than 30 mmHg” and “having at least one MAP value less than 60 mmHg” as the independent variable, respectively.

To explore whether preoperative clinical condition, vulnerability to cerebral vasospasm and treatment modality modified the associations, we repeated all analyses for neurologic outcome at discharge with the following interaction terms: preoperative World Federation of Neurological Surgeons Grading System grade (dichotomized in grades 4 to 5 and grades 1 to 3; see table 1, Supplemental Digital Content 1, <http://links.lww.com/ALN/B791>, listing neurologic scoring systems), timing of

intervention (dichotomized in early [less than or equal to 2 days after the ictus] and late [greater than 2 days after the ictus]) and treatment modality (clipping or coiling).

The aforementioned analyses were repeated for the Glasgow Outcome Scale score at three months as a secondary outcome measure. Bonferroni correction was used to correct for the number of categories within a threshold, and  $P$  values and CIs were reported accordingly. For all other analyses, a  $P$  value less than 0.05 was considered to be statistically significant. All statistical tests were two tailed. The statistical analyses were performed with R (Version 3.3.1; R, Inc., for Macintosh).<sup>32</sup>

## Results

In the study period, 1,484 patients were admitted for aneurysmal subarachnoid hemorrhage, and 1,099 (74.1%) were eligible for inclusion in our analyses (fig. 1). Of these patients, 447 (40.7%) had a poor neurologic outcome at discharge.

According to the local protocol for aneurysmal subarachnoid hemorrhage patients, general anesthesia was maintained with propofol (induction bolus 1 to 3mg/kg, maintenance infusion 4 to 10mg · kg<sup>-1</sup> · h<sup>-1</sup>), an opioid (either sufentanil

or remifentanyl), and a neuromuscular blocking agent (either rocuronium or atracurium). In all patients, noninvasive blood pressure measurements were used. In addition, in all patients undergoing clipping, and by indication in some patients during coiling, blood pressure was measured continuously by using an intra-arterial catheter. Episodes of hypotension were treated with ephedrine, phenylephrine, or norepinephrine (bolus and/or continuous infusion), and episodes of hypertension were generally treated with a mixed  $\alpha$ - and  $\beta$ -adrenergic blocking drug (labetalol) or an  $\alpha_2$ -adrenergic agonist (clonidine).

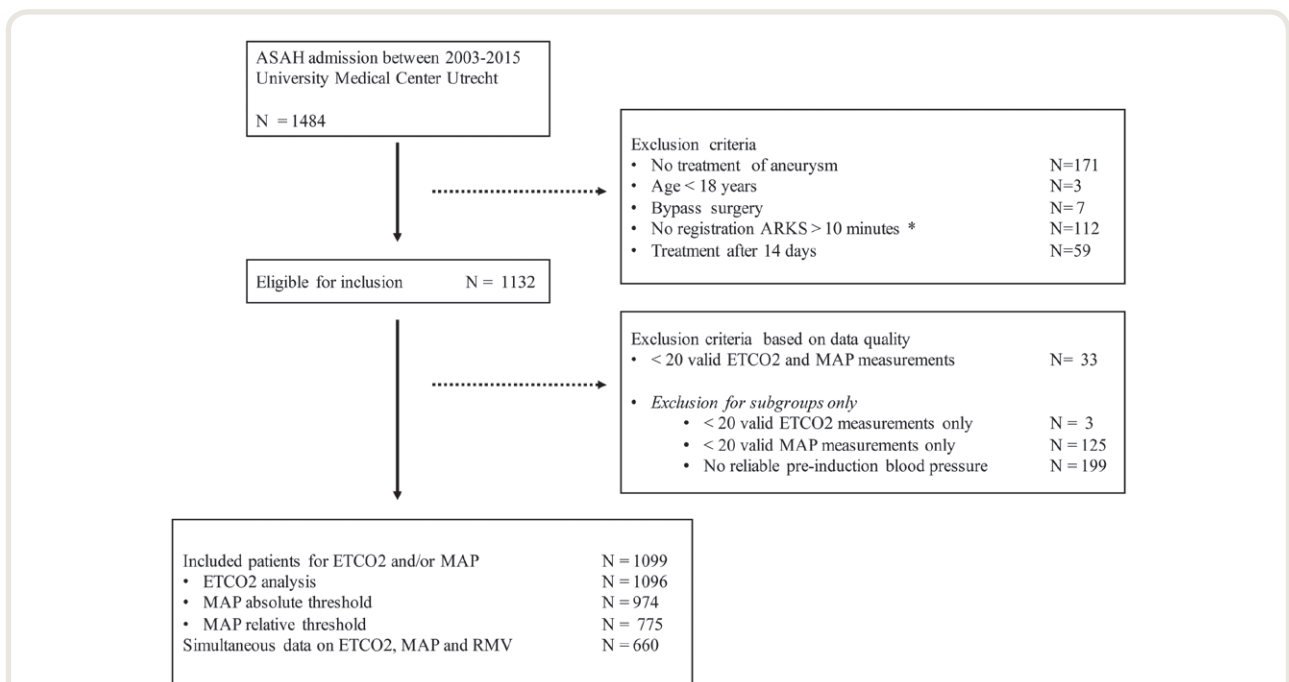
Patient characteristics were compared for patients with a good neurologic outcome and poor neurologic outcome at discharge, and for patients presenting for endovascular coiling and neurosurgical clipping (table 1). Most demographic factors, medical history and preadmission medication, neurologic and periprocedural factors, and complications were associated with neurologic outcome. Patients with a poor neurologic outcome received more norepinephrine during the intervention. There was no significant difference in treatment modality or in procedure and anesthesia time between patients with a good outcome and a poor outcome. Patients treated with endovascular coiling were, on average, older and had a higher American Society of Anesthesiologists Physical Status class. During coiling, phenylephrine was frequently used as a vasopressor, whereas norepinephrine was primarily used during clipping. Patients treated with coiling suffered less from electrolyte

imbalances, anemia, postintervention neurologic decline, and cerebral edema. In addition, they were treated less frequently with cerebrospinal fluid (CSF) drainage (defined as requiring an external ventricular drain, external lumbar drain, or lumbar punctures).

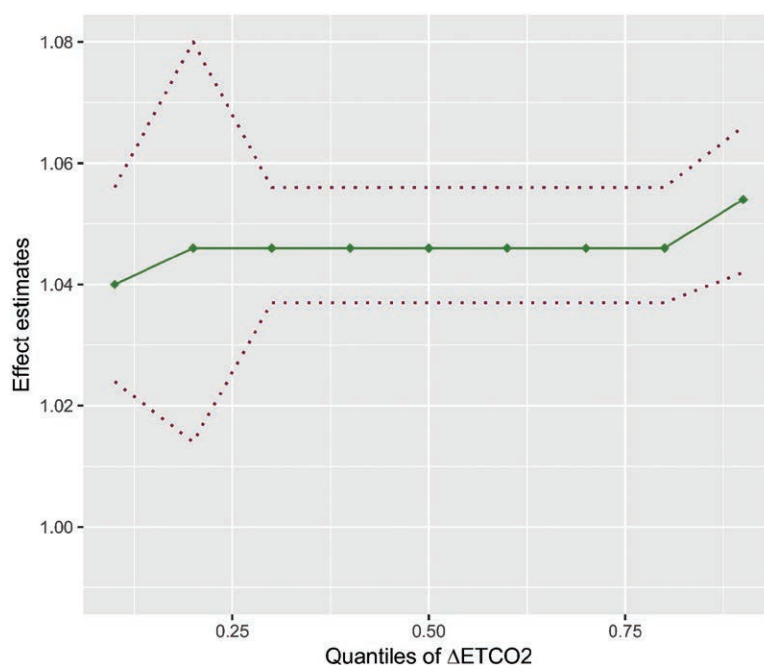
Due to missing values in either  $ETCO_2$  or MAP values, 1,096 patients (99.7%) could be included for analysis of  $ETCO_2$  thresholds, 974 (88.6%) for analysis of absolute MAP thresholds, and 775 (70.5%) could be included for analysis of relative MAP thresholds, because preinduction blood pressure measurements were missing in 199 patients. Data on the extent of missing data and the variables used for multiple imputation are provided in Supplemental Digital Content 4 (<http://links.lww.com/ALN/B794>), as are the results from the univariable complete case analysis for neurologic outcome at discharge to show the impact of imputation on observed estimates.

The median of the mean  $ETCO_2$  was 43 mmHg (interquartile range, 41 to 45) in patients with a good neurologic outcome and 44 mmHg (interquartile range, 42 to 46) in patients with a poor neurologic outcome ( $P < 0.001$ ); the median was 43 mmHg (41 to 45) in patients treated with neurosurgical clipping, and 44 mmHg (42 to 46) in patients who received endovascular coiling ( $P < 0.001$ ).

The median of the mean MAP was 80 mmHg (interquartile range, 72 to 88) and 81 mmHg (interquartile range, 74 to 88) in patients with good neurologic outcome and poor



**Fig. 1.** Flow chart aneurysmal subarachnoid hemorrhage. \*No registration, largely due to (temporary) transfer to other institution for intervention or failure to record for more than 10 consecutive minutes due to disconnection with the ARKS. ASAH, aneurysmal subarachnoid hemorrhage; ARKS, anesthesia record keeping system;  $ETCO_2$ , end-tidal carbon dioxide; MAP, mean arterial blood pressure; RMV, respiratory minute volume.



**Fig. 2.** Association between end tidal carbon dioxide concentrations ( $ET_{CO_2}$ ) and mean arterial pressure (MAP). The effect of changes in MAP on changes in  $ET_{CO_2}$  was studied, using a mixed regression model taking clustering into account. The effect estimates found in the linear quantile mixed regression model were plotted per quantile  $\Delta ET_{CO_2}$ , with their corresponding 95% CI (dotted lines). Within the first quartiles we saw some extreme outliers, explaining the relatively broad CI.

neurologic outcome, respectively ( $P = 0.021$ ). In patients treated with neurosurgical clipping, the median of the mean MAP was 82 (interquartile range, 75 to 89), while the median was 79 (71 to 87) in patients receiving endovascular coiling ( $P < 0.001$ ).

### Association between MAP and $ET_{CO_2}$

In 660 patients (60.1%), paired data for  $ET_{CO_2}$ , MAP, and respiratory minute ventilation were available, meaning that 1 min before an  $ET_{CO_2}$  value was measured, a MAP and respiratory minute ventilation value were registered, to be used to estimate the association between  $ET_{CO_2}$  and MAP. After adjustment for respiratory minute ventilation, the results from the linear quantile mixed regression analysis showed a significant but not clinically relevant association between MAP and  $ET_{CO_2}$ : for most quantiles of  $ET_{CO_2}$ ,  $ET_{CO_2}$  increased with factor 1.05 (95% CI, 1.04 to 1.06;  $P < 0.001$ ) per 10 mmHg increase in MAP (fig. 2).

### Association between $ET_{CO_2}$ , MAP, and Neurologic Outcome

A restricted cubic spline regression analysis with three knots (at the tenth, fiftieth, and ninetieth percentile) resulted in

the best fit. On the basis of distribution of the data and inspection of the spline plots, the independent variables could be grouped into two to seven categories.

Effect estimates for mean  $ET_{CO_2}$  and mean MAP are presented in table 2. None of the categories of mean  $ET_{CO_2}$  and mean MAP were associated with neurologic outcome.

The results from the multivariable analysis using time-weighted average area under the curve thresholds are shown in figure 3 (see table 1 of Supplemental Digital Content 5, <http://links.lww.com/ALN/B795>, for both univariable and multivariable effect estimates for all time-weighted average area under the curve thresholds). After adjustment for potential confounders, there was no association between any of the time-weighted average area under the curve thresholds of  $ET_{CO_2}$  or MAP and neurologic outcome.

The occurrence of extreme values of  $ET_{CO_2}$  (*i.e.*, at least one  $ET_{CO_2}$  value less than 30 mmHg) or MAP (*i.e.*, at least one MAP value less than 60 mmHg) was also not associated with neurologic outcome (table 2). There was no clinically relevant modification of the results by preoperative World Federation of Neurological Surgeons Grading System grade, timing of the intervention (as proxy for vulnerability to cerebral vasospasm) and treatment modality (see tables 1 and 2 in Supplemental Digital Content 6, <http://links.lww.com/ALN/B795>).

**Table 2.** Association between ETco<sub>2</sub>, MAP, and Poor Neurologic Outcome

Threshold and Categories	Poor Outcome at Discharge			Poor Outcome at Three Months		
	Risk Ratio (CI)	P Value	Adjusted Risk Ratio (CI)†	Risk Ratio (CI)	P Value	Adjusted Risk Ratio (CI)‡
<b>N = number of patients with time-weighted average area under the curve or mean &gt; 0</b>						
<b>CI and sign. level for P value are reported per threshold†</b>						
Mean MAP (N = 974; 99.2% CI; significant P < 0.008)						
0.0–0.1 (53–67.8 mmHg)	0.64 (0.33–1.25)	0.077	0.94 (0.63–1.42)	0.60 (0.27–1.29)	0.076	0.87 (0.49–1.54)
0.1–0.25 (67.8–73.2 mmHg)	0.80 (0.45–1.41)	0.305	1.06 (0.79–1.43)	0.65 (0.34–1.25)	0.081	0.90 (0.56–1.45)
0.25–0.5 (73.2–80.6 mmHg)	0.96 (0.59–1.56)	0.838	1.05 (0.81–1.37)	0.91 (0.54–1.55)	0.665	0.98 (0.68–1.42)
0.5–0.75 (80.6–88.3 mmHg)	ref = 1		ref = 1	ref = 1		ref = 1
0.75–0.9 (88.3–95.5 mmHg)	1.22 (0.70–2.15)	0.348	1.16 (0.87–1.53)	1.20 (0.66–2.19)	0.430	1.13 (0.75–1.71)
0.9–1.0 (95.5–138 mmHg)	0.92 (0.48–1.74)	0.732	0.90 (0.64–1.25)	1.03 (0.51–2.07)	0.911	0.98 (0.59–1.64)
Mean ETco <sub>2</sub> (N = 1096; 99.2% CI; significant P < 0.008)						
0.0–0.1 (32–39.6 mmHg)	0.70 (0.38–1.31)	0.133	0.93 (0.65–1.35)	0.70 (0.35–1.41)	0.181	0.97 (0.59–1.62)
0.1–0.25 (39.6–41.3 mmHg)	0.79 (0.46–1.35)	0.248	0.92 (0.68–1.25)	0.53 (0.28–1.01)	0.009	0.62 (0.37–1.05)
0.25–0.5 (41.3–43.5 mmHg)	0.78 (0.49–1.23)	0.150	0.83 (0.64–1.07)	0.79 (0.48–1.32)	0.228	0.77 (0.54–1.10)
0.5–0.75 (43.5–45.6 mmHg)	ref = 1		ref = 1	ref = 1		ref = 1
0.75–0.9 (45.6–47.3 mmHg)	0.95 (0.56–1.62)	0.807	0.95 (0.72–1.26)	0.85 (0.47–1.54)	0.484	0.87 (0.58–1.29)
0.9–1.0 (47.3–56 mmHg)	1.50 (0.83–2.71)	0.073	1.11 (0.82–1.52)	0.98 (0.51–1.88)	0.954	0.83 (0.53–1.32)
Any ETco <sub>2</sub> < 30 mmHg (N = 405; 95% CI; significant P < 0.05)	0.89 (0.69–1.15)	0.381	0.95 (0.81–1.10)	0.88 (0.66–1.17)	0.386	0.89 (0.71–1.13)
Any MAP < 60 mmHg (N = 166; 95% CI; significant P < 0.05)	0.99 (0.70–1.39)	0.954	0.94 (0.78–1.14)	1.16 (0.80–1.67)	0.444	1.00 (0.77–1.31)

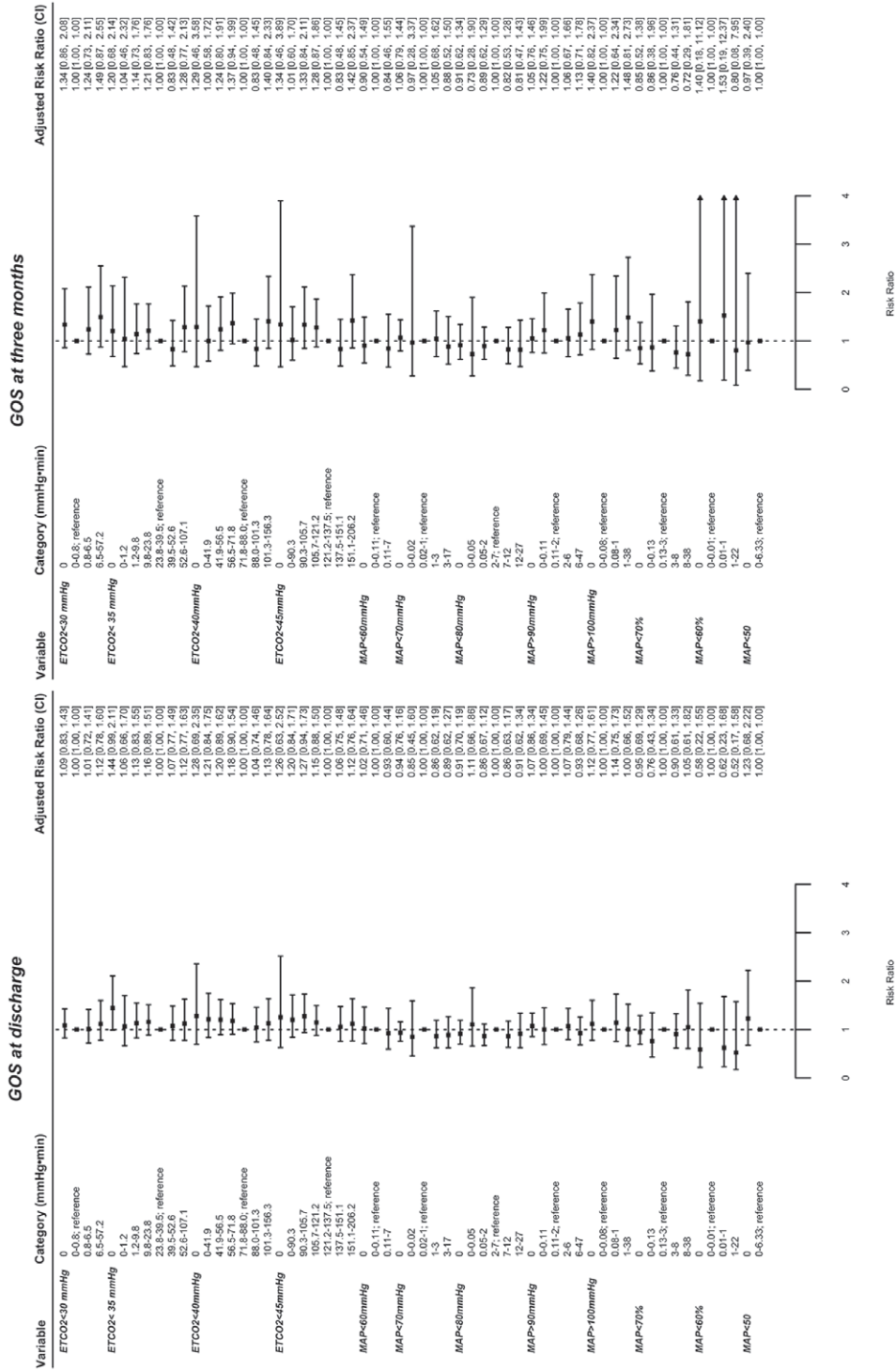
Poor neurologic outcome was defined as a Glasgow Outcome Scale of 1 to 3.

\*Statistically significant.

† Bonferroni correction was used to correct for the number of categories within a threshold and P values and CIs are reported accordingly. For example, when four categories were made within a threshold, P < 0.0125 was considered as statistical significant after a Bonferroni correction (0.05/4), with a corresponding CI of 98.8%. For “any ETco<sub>2</sub> < 30 mmHg” and “any MAP < 60 mmHg” no categories were used, and P < 0.05 was considered statistically significant.

‡ 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 Neurologic 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 neurologic decline, rebleed, edema, cerebral ischemia, hydrocephalus, anemia, extracranial complications, preoperative MAP, amount of ephedrine, phenylephrine and noradrenaline per hour, preoperative oxygenation level, and year of procedure. In addition, the results for the ETco<sub>2</sub> thresholds were adjusted for the mean MAP per case, whereas the results for the MAP thresholds were adjusted for the mean ETco<sub>2</sub> per case. ETco<sub>2</sub>, end-tidal carbon dioxide; MAP, mean arterial blood pressure; Q, quantile; Ref, reference category.





**Fig. 3.** Adjusted risk ratios for all time-weighted average area under the curve thresholds for ETcO<sub>2</sub> and MAP. All reference categories are shown in the plot with an effect estimate of 1.00. Bonferroni correction was used to correct for the number of categories within an independent variable and CIs are reported accordingly. For example: when four categories were made within an independent variable, a P value of < 0.0125 was considered as statistically significant after a Bonferroni correction (0.05/4) with a corresponding CI 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 Neurologic Surgeons Grading System Score on admission, intervention modality (clipping or coiling), day of intervention, number of times receiving general anesthesia before and after the intervention, cerebral spinal fluid drainage, postoperative neurologic decline, rebleed, 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 ETcO<sub>2</sub> thresholds were adjusted for the mean MAP per case, whereas the results for the MAP thresholds were adjusted for the mean ETcO<sub>2</sub> per case. ETcO<sub>2</sub>, end-tidal carbon dioxide; GOS, Glasgow Outcome scale (dichotomized into a good outcome [GOS score 4 to 5] and a poor outcome [GOS score 1 to 3]); MAP, mean arterial blood pressure; Reference, reference category.

lww.com/ALN/B796, for the results from the multivariable analyses for all three interaction terms).

## Discussion

Within the ranges of current clinical practice, *i.e.*, consensus translated into a protocolized institutional strategy, none of the studied  $\text{ETCO}_2$  and MAP ranges were associated with neurologic outcome at discharge, irrespective of the duration below or above the threshold, and irrespective of preoperative clinical condition, timing of treatment or treatment modality. Even extreme hypotension and hypocapnia, still occurring although short of duration, were not associated with poor neurologic outcome.

Several studies described the effect of hyper- and hypocapnia on neurologic outcome after acute cerebral injury, primarily in an intensive care setting. Unfortunately, aneurysmal subarachnoid hemorrhage patients are underrepresented. In patients undergoing endovascular treatment after an acute ischemic stroke, a higher mean  $\text{ETCO}_2$  (mean from values collected every 30 min) during general anesthesia was associated with a better neurologic outcome.<sup>10</sup> In addition, postcardiac arrest  $\text{PaCO}_2$  disturbances were associated with a poor neurologic outcome<sup>11</sup> and prolonged hyperventilation had deleterious effects on the neurologic outcome after traumatic brain injury.<sup>9</sup> Two small studies in poor-grade aneurysmal subarachnoid hemorrhage patients studied the association between carbon dioxide concentrations and neurologic outcome and found that the cerebral perfusion increased when the  $\text{PaCO}_2$  increased.<sup>33,34</sup> Hypercapnia was well tolerated in the presence of continuous CSF drainage (thus eliminating the potential effect of an increased intracranial pressure), while increasing the cerebral perfusion and possibly preventing secondary cerebral ischemia.<sup>33,34</sup> To our knowledge, no studies reported on induced hypercapnia and neurologic outcome in aneurysmal subarachnoid hemorrhage patients without CSF drainage. In contrast with studies reporting a benefit for higher carbon dioxide concentrations, a large retrospective cohort study in patients with acute cerebral injury found that hypercapnia (mean  $\text{PaCO}_2$  52.2 mmHg, mean pH 7.39) was not associated with a better survival to discharge for all patients combined or for subgroups based on diagnosis (traumatic brain injury, stroke [hemorrhagic and ischemic stroke combined], and cardiac arrest). In fact, hypercapnic acidosis (mean  $\text{PaCO}_2$  56.7 mmHg, mean pH 7.19) was associated with an increased risk of in-hospital mortality.<sup>28</sup> Other studies found that spontaneous hyperventilation was associated with a poor neurologic outcome after aneurysmal subarachnoid hemorrhage.<sup>35,36</sup> In contrast with most other studies in the field of acute cerebral injury, we were not able to demonstrate an association between hyper- or hypocapnia and neurologic outcome in aneurysmal subarachnoid hemorrhage patients specifically.

Several studies described the effects of hypotension on neurologic outcome in aneurysmal subarachnoid hemorrhage patients treated with neurosurgical clipping. To our knowledge, no such studies were conducted in aneurysmal subarachnoid hemorrhage patients undergoing endovascular coiling. One retrospective study of 164 aneurysmal subarachnoid hemorrhage patients receiving neurosurgical clipping suggested that a decrease in blood pressure of more than 50% was associated with a poor outcome. After adjusting for age and the World Federation of Neurologic Surgeons Grading System,<sup>37</sup> these results were no longer significant.<sup>5</sup> Another retrospective study in 398 aneurysmal subarachnoid hemorrhage patients receiving neurosurgical clipping, defined intraoperative hypotension as a reduction of 30 mmHg or at least 20% of the initial SBP, for at least 15 min. Intraoperative hypotension was an independent risk factor for the development of a postoperative cerebral infarction (odds ratio, 3.016; 95% CI, 1.285 to 7.075).<sup>6</sup> A study in 84 patients found a comparable association for intraoperative hypotension defined as a SBP less than 90 mmHg for more than 15 min.<sup>7</sup> Other studies found an association between deliberately induced hypotension in aneurysmal subarachnoid hemorrhage patients undergoing neurosurgical clipping and a poor neurologic outcome.<sup>38,39</sup> The current study did not look into the effects of relatively mild hypotension (decrease of 20% from the baseline) or SBP, but did not find any association for slightly more severe hypotension (MAP less than 30% from baseline or more) and neurologic outcome, nor did it find an association for any of the absolute MAP thresholds and neurologic outcome. Previous studies have found an association between preinduction and intraoperative hypertension, and a poor neurologic outcome.<sup>38,39</sup> Initiation of hypertension to prevent delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage patients admitted at the intensive care unit was not supported by any evidence.<sup>40</sup> The present study found no association between intraoperative hypertension and neurologic outcome after clipping or coiling of a ruptured aneurysm.

## Strengths and Limitations

This study has several strengths. First, it is one of the larger studies relating intraoperative blood pressure and carbon dioxide ranges in aneurysmal subarachnoid hemorrhage patients to neurologic outcome thus far, enabling us to find relatively small effects when present. Second, in contrast to previous studies, patients undergoing endovascular coiling were also included, making the results applicable to a larger group of aneurysmal subarachnoid hemorrhage patients, especially since endovascular treatment has become the recommended treatment entity when technically amendable.<sup>2</sup> Third, we used time-weighted average area under the curve as a measure to summarize the course of  $\text{ETCO}_2$  and MAP in an elaborate manner, containing

not only the distance from, but also the duration below (or above) the threshold. Fourth, the results of this study are adjusted for many potential confounders, including comorbidities and postoperative complications. This may explain why we did not find an association between MAP and  $\text{ETCO}_2$  ranges and neurologic outcome, while some of the previous studies did. All the previously conducted studies were smaller in sample size and were not able to include as many confounders, and therefore, results may have been influenced by residual confounding.

Nevertheless, this study has some obvious limitations. First,  $\text{PaCO}_2$  and pH, rather than  $\text{ETCO}_2$ , influence the cerebral perfusion.<sup>8,28</sup> Unfortunately, we were unable to calibrate  $\text{ETCO}_2$  concentrations with  $\text{PaCO}_2$  (and pH) values, since the time points of blood sampling could not be linked to the corresponding  $\text{ETCO}_2$  values. In patients presenting for elective craniotomies, small  $\text{PaCO}_2$ – $\text{ETCO}_2$  gradients around 4 mmHg were reported,<sup>41</sup> meaning that in the present studies,  $\text{PaCO}_2$  concentrations may be slightly higher than the reported  $\text{ETCO}_2$  values. We may therefore overestimate the effect of hypercapnia, while underestimating the effect of hypocapnia. However, with the reported small gradient of 4 mmHg, we believe this is of limited effect. Second, we used the Glasgow Outcome Scale at discharge as our primary outcome measure. As improvement of functional outcome can continue even after the first year of aneurysmal subarachnoid hemorrhage,<sup>42</sup> the results of this study may not apply to long-term neurologic outcome. Third, the time-weighted average area under the curve is not easily applicable and interpretable in clinical practice. However, cohort studies in patients presenting for noncardiac surgery have shown that a (time-weighted average) area under the curve can successfully be used to summarize intraoperative blood pressure levels for research purposes.<sup>19,30,43</sup> Fourth, despite the relatively large sample size, some of the  $\text{ETCO}_2$  and MAP categories contained a relatively small number of patients, which may have resulted in a lack of power to detect differences. Fifth, although we adjusted the results for a large set of potential confounders, residual confounding might be present due to the retrospective nature of this study. In addition, we were not able to collect data on the presence of cerebral vasospasm during the intervention. Sixth, we had to deal with missing data. We imputed all variables except for the independent variables, because for these variables, we already had extrapolated values from the median value per minute to obtain a time-weighted average area under the curve. The imputation had little effect on the effect estimates (see table 2, Supplemental Digital Content 4, <http://links.lww.com/ALN/B794>, showing results for the univariable Poisson regression analyses for neurologic outcome at discharge for the complete cases and the imputed data). Finally, potential reasons for anesthesiologists to aim for certain MAP and  $\text{ETCO}_2$  ranges were not documented.

However, anesthesiologists were also not influenced by the conduct of this study.

## Clinical Implications

Despite sparse evidence, international guidelines currently recommend a SBP less than 160 to 180 mmHg until the aneurysm is obliterated.<sup>2,44</sup> Once the aneurysm is secured, higher blood pressures are allowed, but it is unknown what exact thresholds should be aimed for.<sup>2</sup> A survey among European neuroanesthesiologists and neurocritical care physicians showed that there is no agreement on that point.<sup>45</sup> At present, there are no guidelines on  $\text{ETCO}_2$  management in aneurysmal subarachnoid hemorrhage patients.

The present study did not demonstrate an association between any of the  $\text{ETCO}_2$  or MAP ranges observed in current clinical practice and neurologic outcome at discharge. We therefore may conclude that a low  $\text{ETCO}_2$  and a low or high MAP might not be as bad as expected. However, this needs some nuance. Anesthesiologists most likely worked in adherence to current guidelines and standard clinical practice, focusing on an  $\text{ETCO}_2$  of 35 to 45 mmHg and a MAP greater than 80 mmHg, with a SBP less than 180 mmHg before and less than 220 mmHg after securing the aneurysm. As a result, extreme values were relatively rare (*e.g.*, only 166 patients had at least one MAP value less than 60 mmHg, see table 1 in Supplemental Digital Content 5, <http://links.lww.com/ALN/B795>, where the number of patients reaching a certain threshold is shown in the first column). This study therefore does not show that we can abandon strict  $\text{ETCO}_2$  and blood pressure regulation; it merely shows that in the context of current clinical practice, no further subgroups of  $\text{ETCO}_2$  and MAP values increased the chance of a good neurologic outcome at discharge. Larger multicenter, and especially prospective, studies are required to further study the effect of  $\text{ETCO}_2$  and MAP on short- and long-term neurologic outcomes. In addition, intraoperative  $\text{ETCO}_2$  concentrations and MAP levels might only be a minor part of a very large and complex puzzle, determining neurologic outcome after a subarachnoid hemorrhage.

## Conclusion

Intraoperative hypocapnia, hypotension, and hypertension, as they occur in clinical practice during cerebral aneurysm clipping or coiling, are not associated with a poor neurologic outcome. However, there is insufficient evidence available to abandon currently used target ranges for  $\text{ETCO}_2$  and blood pressure.

## Acknowledgments

The authors thank Wietze Pasma, D.V.M. (Department of Anesthesiology, University Medical Center Utrecht, Utrecht

University, The Netherlands) and Jacqueline L.P. Vromen, Ph.D. (Department of Anesthesiology, University Medical Center Utrecht, Utrecht University, The Netherlands) for their contribution in data collection.

## Research Support

Support was provided solely from departmental sources.

## Competing Interests

The authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Akkermans: University Medical Center Utrecht, Department of Anesthesiology, Heidelberglaan 100, Local mail: Q04.2.313 P.O. Box 85500, 3508 GA Utrecht, The Netherlands. a.akkermans@umcutrecht.nl. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

## References

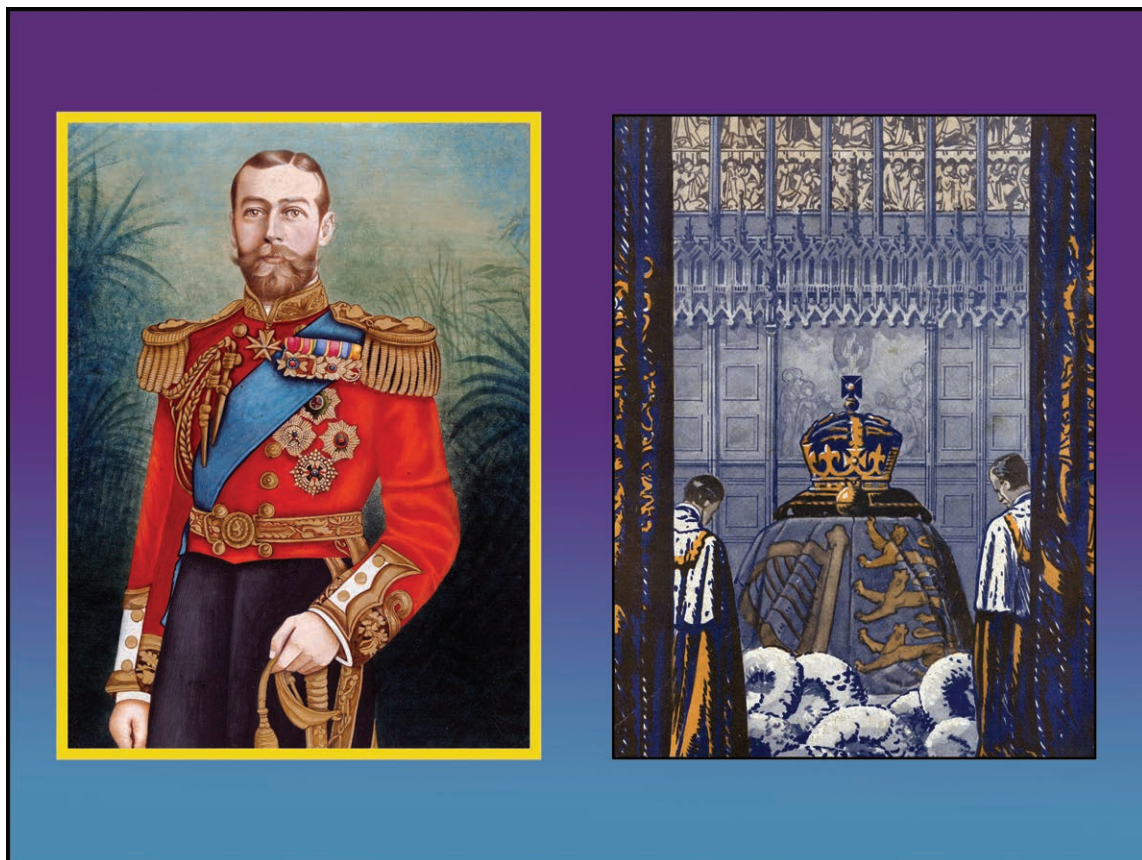
1. Suarez JI, Tarr RW, Selman WR: Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006; 354:387–96
2. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; 43:1711–37
3. Nieuwkamp DJ, de Wilde A, Wermer MJ, Algra A, Rinkel GJ: Long-term outcome after aneurysmal subarachnoid hemorrhage—risks of vascular events, death from cancer and all-cause death. *J Neurol* 2014; 261:309–15
4. Pasternak JJ, Lanier WL: Neuroanesthesiology update. *J Neurosurg Anesthesiol* 2015; 27:87–122
5. Hoff RG, Van Dijk GW, Mettes S, Verweij BH, Algra A, Rinkel GJ, Kalkman CJ: Hypotension in anaesthetized patients during aneurysm clipping: Not as bad as expected? *Acta Anaesthesiol Scand* 2008; 52:1006–11
6. Chong JY, Kim DW, Jwa CS, Yi HJ, Ko Y, Kim KM: Impact of cardio-pulmonary and intraoperative factors on occurrence of cerebral infarction after early surgical repair of the ruptured cerebral aneurysms. *J Korean Neurosurg Soc* 2008; 43:90–6
7. Chang HS, Hongo K, Nakagawa H: Adverse effects of limited hypotensive anesthesia on the outcome of patients with subarachnoid hemorrhage. *J Neurosurg* 2000; 92:971–5
8. Curley G, Kavanagh BP, Laffey JG: Hypocapnia and the injured brain: More harm than benefit. *Crit Care Med* 2010; 38:1348–59
9. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg* 1991; 75:731–9
10. Takahashi CE, Brambrink AM, Aziz MF, Macri E, Raines J, Multani-Kohol A, Hinson HE, Lutsep HL, Clark WM, Fields JD: Association of intraprocedural blood pressure and end tidal carbon dioxide with outcome after acute stroke intervention. *Neurocrit Care* 2014; 20:202–8
11. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S: Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. *Circulation* 2013; 127:2107–13
12. Way M, Hill GE: Intraoperative end-tidal carbon dioxide concentrations: What is the target? *Anesthesiol Res Pract* 2011; 2011:271539
13. Marhong J, Fan E: Carbon dioxide in the critically ill: Too much or too little of a good thing? *Respir Care* 2014; 59:1597–605
14. Hovorka J: Carbon dioxide homeostasis and recovery after general anaesthesia. *Acta Anaesthesiol Scand* 1982; 26:498–504
15. Elm E von, Altman D, Egger M, Pocock S, Gøtzsche P, Vandenbroucke J: STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61:344–9
16. Jennett B, Bond M: Assessment of outcome after severe brain damage. A practical scale. *Lancet* 1975; 305:480–4
17. Mascha EJ, Yang D, Weiss S, Sessler DI: Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. *ANESTHESIOLOGY* 2015; 123:79–91
18. Bijker JB, Klei WA van, Kappen TH, Wolfswinkel L van, Moons KGM, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition. *ANESTHESIOLOGY* 2007; 107:213–20
19. van Waes JA, van Klei WA, Wijeyesundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS: Association between intraoperative hypotension and myocardial

- injury after vascular surgery. *ANESTHESIOLOGY* 2016; 124:35–44
20. van Klei WA, van Waes JA, Pasma W, Kappen TH, van Wolfswinkel L, Peelen LM, Kalkman CJ: Relationship between preoperative evaluation blood pressure and preinduction blood pressure: A cohort study in patients undergoing general anesthesia. *Anesth Analg* 2017; 124:431–7
  21. Kool NP, van Waes JA, Bijker JB, Peelen LM, van Wolfswinkel L, de Graaff JC, van Klei WA: Artifacts in research data obtained from an anesthesia information and management system. *Can J Anaesth* 2012; 59:833–41
  22. Bender SP, Paganelli WC, Gerety LP, Tharp WG, Shanks AM, Housey M, Blank RS, Colquhoun DA, Fernandez-Bustamante A, Jameson LC, Khetarpal S: Intraoperative lung-protective ventilation trends and practice patterns: A report from the multicenter perioperative outcomes group. *Anesth Analg* 2015; 121:1231–9
  23. Donders AR, van der Heijden GJ, Stijnen T, Moons KG: Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; 59:1087–91
  24. Buuren S Van, Groothuis-Oudshoorn K: Multivariate imputation by chained equations. *J Stat Softw* 2011; 45:1–67
  25. Rubin DB: *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons, New York, 1987
  26. Little RJA: Regression with missing x's: A review. *J Am Stat Assoc* 1992; 87:1227–37
  27. Ornato JP, Garnett AR, Glauser FL: Relationship between cardiac output and the end-tidal carbon dioxide tension. *Ann Emerg Med* 1990; 19:1104–6
  28. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M: Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury. *JAMA Neurol* 2018; Mar 19:1–9
  29. Knol MJ, Le Cessie S, Algra A, Vandembroucke JP, Groenwold RH: Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. *CMAJ* 2012; 184:895–9
  30. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A: Relationship between intraoperative hypotension, thresholds, and acute kidney and myocardial injury after noncardiac surgery. A retrospective cohort analysis. *ANESTHESIOLOGY* 2017; 126:47–65
  31. Harrell FE Jr, Lee KL, Pollock BG: Regression models in clinical studies: Determining relationships between predictors and response. *J Natl Cancer Inst* 1988; 80:1198–202
  32. R Core Team (2016). R: A language and environment for statistical computing. Available at <https://www.r-project.org/>
  33. Westermaier T, Stetter C, Kunze E, Willner N, Holzmeier J, Kilgenstein C, Lee JY, Ernestus RI, Roewer N, Muellenbach RM: Controlled transient hypercapnia: A novel approach for the treatment of delayed cerebral ischemia after subarachnoid hemorrhage? *J Neurosurg* 2014; 121:1056–62
  34. Westermaier T, Stetter C, Kunze E, Willner N, Holzmeier J, Weiland J, Koehler S, Lotz C, Kilgenstein C, Ernestus RI, Roewer N, Muellenbach RM: Controlled hypercapnia enhances cerebral blood flow and brain tissue oxygenation after aneurysmal subarachnoid hemorrhage: Results of a phase 1 study. *Neurocrit Care* 2016; 25:205–14
  35. Williamson CA, Sheehan KM, Tipirneni R, Roark CD, Pandey AS, Thompson BG, Rajajee V: The association between spontaneous hyperventilation, delayed cerebral ischemia, and poor neurological outcome in patients with subarachnoid hemorrhage. *Neurocrit Care* 2015; 23:330–8
  36. Solaiman O, Singh JM: Hypocapnia in aneurysmal subarachnoid hemorrhage: Incidence and association with poor clinical outcomes. *J Neurosurg Anesthesiol* 2013; 25:254–61
  37. Rosen DS, Macdonald RL: Subarachnoid hemorrhage grading scales: A systematic review. *Neurocrit Care* 2005; 2:110–8
  38. Ayling OGS, Ibrahim GM, Drake B, Torner JC, Macdonald RL: Operative complications and differences in outcome after clipping and coiling of ruptured intracranial aneurysms. *J Neurosurg* 2015; 123:1–8
  39. Mahaney KB, Todd MM, Bayman EO, Torner JC; IHAST Investigators: Acute postoperative neurological deterioration associated with surgery for ruptured intracranial aneurysm: Incidence, predictors, and outcomes. *J Neurosurg* 2012; 116:1267–78
  40. Gathier CS, van den Bergh WM, van der Jagt M, Verweij BH, Dankbaar JW, Müller MC, Oldenbeuving AW, Rinkel GJE, Slooter AJC; HIMALAIA Study Group: Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: A randomized clinical trial. *Stroke* 2018; 49:76–83
  41. Husaini J, Choy YC: End-tidal to arterial carbon dioxide partial pressure difference during craniotomy in anaesthetised patients. *Med J Malaysia* 2008; 63:384–7
  42. Samra SK, Giordani B, Caveney AF, Clarke WR, Scott PA, Anderson S, Thompson BG, Todd MM; CFAAST Investigators: Recovery of cognitive function after surgery for aneurysmal subarachnoid hemorrhage. *Stroke* 2007; 38:1864–72
  43. Vernooij LM, Klei WA Van, MacHina M, Pasma W, Peelen LM: Different methods of modeling hypotension and their association with postoperative troponin elevation in patients undergoing noncardiac surgery. *Br J Anaesth* 2018; 120:1080–9

44. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G; European Stroke Organization: European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013; 35:93–112
45. Velly LJ, Bilotta F, Fàbregas N, Soehle M, Bruder NJ, Nathanson MH; European Neuroanaesthesia and Critical Care Interest Group (ENIG): Anaesthetic and ICU management of aneurysmal subarachnoid haemorrhage: A survey of European practice. *Eur J Anaesthesiol* 2015; 32:168–76

## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# Morphine, Cocaine, and the Euthanasia of King George V



In a 1924 contribution to *Lancet*, Dr. F. G. Chandler extolled the value of “Cocaine in Euthanasia,” particularly for patients who were terminal with pulmonary tuberculosis. A dozen years later, British King George V (1865 to 1936, *left*) was terminally bronchitic, bedridden, and passing repeatedly in and out of consciousness. Shortly after 11 PM on January 20, 1936, the Physician-in-Ordinary to the King administered a pair of lethal doses intravenously, to hasten the struggling monarch’s demise. This regicide was only revealed a half century later in the diary of the euthanizer, Lord Dawson of Penn (1864 to 1945), who penned: “I therefore decided to determine the end and injected (myself) morphia gr. 3/4 and shortly afterwards cocaine gr. 1 into the [King’s] distended jugular vein....” (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

*George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.*