ANESTHESIOLOGY

# Carbon Dioxide, Blood Pressure, and Perioperative Stroke: A Retrospective Case–Control Study

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- There is a high incidence of perioperative stroke in some patients
- Hypotension may lead to cerebral ischemia, and the impact on cerebral perfusion may be greater in the setting of hypercapnia or hypocapnia

### What This Article Tells Us That Is New

- In a case–control study using the Multicenter Perioperative Outcomes Group data, hypocarbia, hypercarbia, and hypotension were each independently associated with postoperative stroke

## ABSTRACT

**Background:** The relationship between intraoperative physiology and postoperative stroke is incompletely understood. Preliminary data suggest that either hypo- or hypercapnia coupled with reduced cerebrovascular inflow (*e.g.*, due to hypotension) can lead to ischemia. This study tested the hypothesis that the combination of intraoperative hypotension and either hypo- or hypercarbia is associated with postoperative ischemic stroke.

**Methods:** We conducted a retrospective, case–control study *via* the Multicenter Perioperative Outcomes Group. Noncardiac, nonintracranial, and nonmajor vascular surgical cases (18 yr or older) were extracted from five major academic centers between January 2004 and December 2015. Ischemic stroke cases were identified *via* manual chart review and matched to controls (1:4). Time and reduction below key mean arterial blood pressure thresholds (less than 55 mmHg, less than 60 mmHg, less than 65 mmHg) and outside of specific end-tidal carbon dioxide thresholds (30 mmHg or less, 35 mmHg or less, 45 mmHg or greater) were calculated based on total area under the curve. The association between stroke and total area under the curve values was then tested while adjusting for relevant confounders.

**Results:** In total, 1,244,881 cases were analyzed. Among the cases that screened positive for stroke (n = 1,702), 126 were confirmed and successfully matched with 500 corresponding controls. Total area under the curve was significantly associated with stroke for all thresholds tested, with the strongest combination observed with mean arterial pressure less than 55 mmHg (adjusted odds ratio per 10 mmHg-min, 1.17 [95% CI, 1.10 to 1.23], $P < 0.0001$) and end-tidal carbon dioxide 45 mmHg or greater (adjusted odds ratio per 10 mmHg-min, 1.11 [95% CI, 1.10 to 1.11], $P < 0.0001$). There was no interaction effect observed between blood pressure and carbon dioxide.

**Conclusions:** Intraoperative hypotension and carbon dioxide dysregulation may each independently increase postoperative stroke risk.

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Stroke is a potentially devastating surgical complication, with an incidence of up to 3% in high-risk noncardiac surgery populations.[1,2] Recent observational data also indicate that the risk of perioperative stroke, as detected by magnetic resonance imaging rather than clinical criteria, may be as high as 7% for older patients after noncardiac surgery.[3] Furthermore, postoperative stroke recognition is often delayed, and thrombolytic interventions are less commonly performed for surgical patients compared with stroke patients in the community setting.[4,5] Given the increased mortality, major disability, delayed diagnosis and treatment, and prolonged hospitalization,[1,4,5] identification of modifiable risk factors for perioperative stroke is of paramount importance.

Although several comorbidity-based preoperative risk factors have been identified,[1,6] there is a paucity of known intraoperative risk factors that may be modifiable. One such candidate risk factor is cerebral malperfusion. Emerging data suggest that intraoperative mean arterial pressure (MAP) may commonly fall below autoregulatory thresholds that maintain cerebral blood flow.[7,8] The combination of reduced cerebral perfusion (*e.g.*, due to hypotension and compromised autoregulation) and impaired vasodilatory reserve (*e.g.*, mediated by hypo- and hypercapnia) creates conditions for cerebral ischemia.[9] Indeed, functional magnetic resonance imaging data demonstrate that such vascular malperfusion can occur in watershed regions during periods of carbon dioxide dysregulation.[10] However, these data have been derived primarily from human volunteers, and it remains unclear whether the combination of hypotension and either hypo- or hypercarbia contributes to stroke risk in a surgical setting.

The primary objective of this study was therefore to determine the relationship between major perturbations in end-tidal carbon dioxide ($ETCO_2$), intraoperative hypotension, and postoperative ischemic stroke. Specifically, this study tested the hypothesis that the combination of intraoperative hypo- or hypercarbia and intraoperative hypotension—defined by specified total area under the curve thresholds—is associated with postoperative stroke. A multicenter electronic health record registry—with detailed intraoperative physiologic data—was used for retrospective data extraction.[11] A secondary objective was to identify stroke characteristics such as etiology, vascular territory affected, severity, management strategy, and outcomes.

## Materials and Methods

### Study Design and Overview

This was a multicenter, retrospective, observational case–control study. Institutional review board exemption approval (HUM00176953) was obtained from the University of Michigan Medical School (Ann Arbor, Michigan), which served as the coordinating study site. The institutional review board of each member organization also approved aggregation of this limited data set into the Multicenter Perioperative Outcomes Group centralized data repository. Written informed consent by the human participants was waived. The study protocol, which included a data and statistical analysis plan, was approved by the Multicenter Perioperative Outcomes Group Perioperative Clinical Research Committee and posted on a publicly accessible server before any data analysis.[12] The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[13] and Reporting of studies Conducted using Observational Routinely-collected health data statement extension (Supplemental Digital Content 1, http://links.lww.com/ALN/C908).[14]

### Study Population

*Inclusion Criteria.* This study included adult (18 yr or older) patients presenting for noncardiac, nonintracranial, and nonmajor vascular surgeries at five large academic medical centers from January 1, 2004, through December 31, 2015. Cases from one institution were included only after June 31, 2009, because of a published study that included postoperative stroke data before this date.[15] Procedures requiring an

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inpatient stay were included, as were emergency and outpatient cases.

*Exclusion Criteria.* All intracranial neurosurgical cases were excluded, as were major cardiac and vascular procedures (*e.g.*, proximal aortic), based on intrinsic procedural risk of stroke. Oral–maxillofacial cases involving penetrating trauma and gunshot wounds to the face and skull were also excluded. All trauma cases involving multiple organ injury, traumatic brain injury, closed head injuries, and penetrating trauma to the neck were also excluded. Last, patients with an American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status classification of VI were excluded. Specific procedural exclusions were performed upon the basis of anesthesia Current Procedural Terminology codes (Supplemental Digital Content 2, http://links.lww.com/ALN/C909).

## Primary Outcome

The primary outcome of this study was perioperative ischemic stroke, defined as any new-onset cerebrovascular infarction that occurred within 30 days after surgery. Stroke outcomes were screened using billing code data for the following International Classification of Diseases, Ninth Revision codes: 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 997.02 (without a diagnostic code indicative of hemorrhage, 430 to 432; see Supplemental Digital Content 2 for code definitions, http://links.lww.com/ALN/C909). Cases that screened positively for stroke then underwent manual chart review to confirm stroke diagnosis based on clinical notes and neuroimaging. For performing the chart review, a physician representative from each site reviewed the medical record. Neurology consultation notes and neuroradiologic reports were reviewed first, and then primary service and other consultation notes were reviewed. Stroke cases were recorded based on a stroke diagnosis reported in these records within 30 days after surgery. A subset of controls (25% from each institution) also underwent manual chart review to confirm the absence of perioperative stroke.

## Data Source

Surgical case data were extracted from the Multicenter Perioperative Outcomes Group Database (an electronic health record–derived registry with detailed physiologic and billing code data[11]) and from electronic medical record systems at each respective institution. Data from each Multicenter Perioperative Outcomes Group site are routinely uploaded to a secure, centralized database. Standardized methods used for data input, storage, quality assurance, and extraction have been described previously.[11] Of note, the initial count of 1,244,881 cases (fig. 1) represents all cases available at the final stages of study analysis. The total number of cases available from all study sites was lower in the earlier stages of the study when stroke cases were initially screened and identified (see fig. 1 legend for additional detail). For intraoperative data extraction, the intraoperative time period was defined from anesthesia start to anesthesia end. Last, stroke characteristics were identified by manual extraction from the electronic medical record from each site. These data include etiology (when available), vascular territory, management, and outcomes as available.

## Exposure Variables

The primary exposure variables of interest were the total area under the curve of intraoperative $ETCO_2$ and MAP thresholds. The total area under the curve is a continuous measure of the area between the empirical cumulative "curve" of a physiologic measure and the specified threshold.[16]

Specific thresholds were chosen and calculated using a previously described methodology.[16] The lower $ETCO_2$ limit was 30 mmHg or less because cerebrovascular resistance is maximally increased (and thus, cerebral blood flow is impaired) with $ETCO_2$ values of approximately 30 mmHg.[17,18] Conversely, high $ETCO_2$ may lead to steal phenomenon, particularly in patients with cerebral arteriosclerosis.[9] Thus, associations with high $ETCO_2$ were also tested for stroke risk. $ETCO_2$ values in the mid-40s (mmHg) and greater are associated with maximally reduced cerebrovascular resistance and increased blood flow.[18] Duration of time that intraoperative MAP is less than 55 mmHg is associated with end-organ injury[19] and was thus chosen as the threshold for the primary blood pressure analysis. Overall, total area under the curve was chosen to determine both the time and degree to which $ETCO_2$ and MAP values were below (or outside of) these thresholds. Details for calculating total area under the curve, along with artifact reductions strategies, are available in Supplemental Digital Content 3 (http://links.lww.com/ALN/C910).

## Case–Control Matching

A case–control matching approach was taken for the current study because of the following advantages. First, case–control studies permit efficient resource allocation to refining exposure assessment and obtaining data on potential confounding factors, particularly for low-incidence outcomes.[20] Second, matching can be used to increase effect-size precision with measures of interest.[21] Last, matching provides marginal estimation, which is often the same technique used for reporting clinical trial treatment effects and is appropriate for population-level estimates.[22]

Stroke cases were matched 1:4 to controls using an optimal matching approach. First, the Mahalanobis distance was assessed between stroke cases and controls, considering each stroke case as a reference point. Mahalanobis distance pairs cases based on a scale-free Euclidean distance, whereby the distance between cases is reduced with increasing covariate similarity. This represents an optimized approach

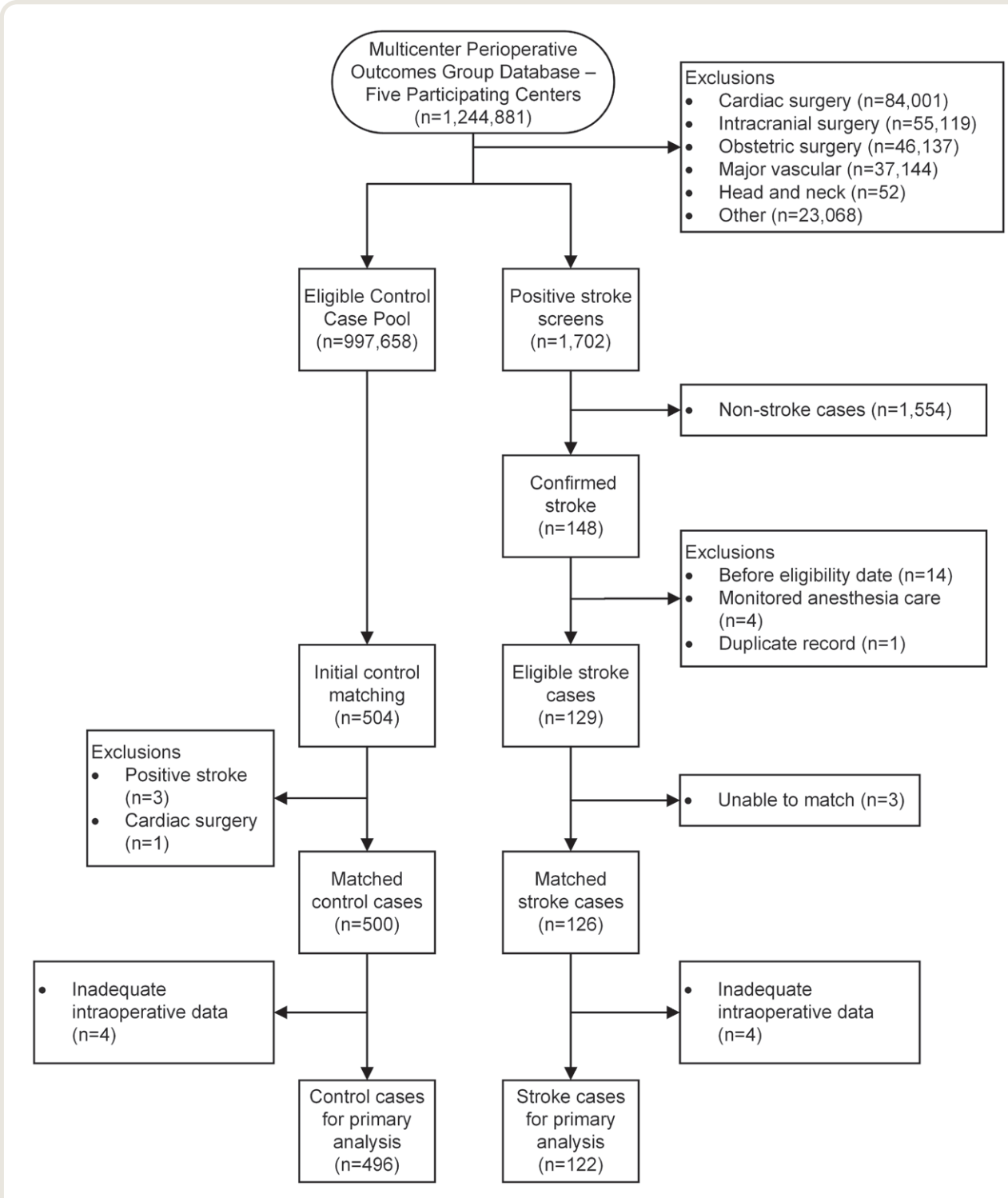


**Fig. 1.** Study flow diagram presented. Of note, this flow diagram is not meant to accurately depict stroke incidence, as stroke cases were initially screened and identified before control cases, when there were fewer cases overall in the Multicenter Perioperative Outcomes Group Database. Additional cases were then added to the database when control cases were later identified and matched.

for continuous exposure variables (*e.g.*, MAP, $ETCO_2$).[23] Principal component scores for each point (stroke and controls) were calculated using original scoring coefficients. Then Euclidean distance from each transformed control to the reference point (stroke case) was estimated. Once the distance measure was selected, the k-means nearest neighbor

matching algorithm was used without replacement to identify the closest control to each case. All matched controls were then removed from the available matching pool, and the nearest neighbor matching algorithm was conducted again using the controls remaining. Matching continued in this manner until up to four controls were matched. The matching process was performed within each institution based on joint distribution of age, height, weight, sex, and blood loss (given the effect of hemorrhage and hemodilution on cerebrovascular ischemia risk[24]). The following comorbidities were also incorporated into the matching process based on associations with stroke and determined using Elixhauser coding algorithms: atrial fibrillation, coronary artery disease, chronic heart failure, chronic kidney disease, chronic pulmonary disease, diabetes, hypertension, and neurologic disorders.[1,6,25,26] Neurologic disorders incorporated within these coding algorithms (*e.g.*, neurodegenerative disorders, multiple sclerosis, epilepsy) have been previously associated with stroke.[27–29] Last, the matched sample was compared on variable distributions using absolute standardized differences.

### Statistical Analysis

Exploratory data analysis techniques were first used to assess the distribution of dependent and independent measures. Descriptive statistics were used for comparing stroke cases and controls in the matched cohort. Means ± SDs, medians (interquartile ranges), and frequencies with percentages were reported as appropriate.

Next, a technique termed seemingly unrelated regression modeling[30] was used to test the relationship between stroke and physiologic variables of interest (*e.g.*, MAP, $ETCO_2$). These models are designed specifically for analysis of variables that may be related, such as MAP and $ETCO_2$ (*i.e.*, in the setting of reduced cardiac output), through contemporaneous cross-equation error correlation, whereby the error terms in the regression equations are correlated. This approach allows the modeling of both exposures in two separate simultaneous equations while avoiding estimation problems relating to multicollinearity. These models can also detect associations too weak to detect with standard logistic models, which are highly sensitive to multicollinearity.[30–32] Seemingly unrelated models were thus constructed with stroke as the dependent variable, and the primary variables of interest—MAP and $ETCO_2$ total area under the curve—as continuous independent variables. The primary analysis included total area under the curve with MAP less than 55 mmHg and $ETCO_2$ 30 mmHg or less followed by $ETCO_2$ 35 mmHg or less and $ETCO_2$ 45 mmHg or greater as a separate, secondary analysis. An additional secondary analysis included the following: total area under the curve of MAP less than 60 mmHg and MAP less than 65 mmHg, both with the same $ETCO_2$ thresholds. These variables were assessed for nonlinearity using splines, as appropriate. Last, models were adjusted for the same variables mentioned in the matching process and time (year). MAP and $ETCO_2$ thresholds were then tested for interaction effects by including the exposure combination in one model and comparing the results to a second model without the combination.[33] Marginal estimates were then assessed using the Wald test with cross-model covariance structure.

Model measures of effect were reported as adjusted odds ratios and 95% Wald CIs. Quasi-likelihood under the independence model criterion was the statistic of choice for goodness-of-fit.[34,35] *P* values less than 0.05 and 95% CI that excluded 1 denoted statistical significance. Analyses were conducted with SAS version 9.4 (SAS Institute, USA).

## Results

The study flow is presented in figure 1. In total, 126 eligible stroke cases were identified and successfully matched to controls. Four cases were then removed because they did not have adequate intraoperative data for analysis. This left 122 final stroke cases for the final primary analysis. Baseline characteristics are presented in table 1. Cohort imbalances were observed for race and American Society of Anesthesiologists Physical Status.

### Carbon Dioxide, Blood Pressure, and Stroke

Descriptive statistics are presented for each $ETCO_2$ and MAP threshold in table 2. After adjusting for pertinent demographic and comorbidity confounders, there were significant associations between stroke and all MAP and $ETCO_2$ thresholds tested (table 3). The strongest associations were observed with total area under the curve thresholds less than MAP 55 mmHg, which conferred an approximately 10 to 17% increased relative risk of stroke per 10 units (mmHg-min) (table 3). Similar associations were present for $ETCO_2$ 30 or less and 45 mmHg or greater, which conferred an approximately 7% and 10% increased relative risk of stroke per 10 units (mmHg-min), respectively. There was no interaction effect observed between MAP and $ETCO_2$ in relation to stroke (Supplemental Digital Content 4, http://links.lww.com/ALN/C911).

### Stroke Characteristics

Descriptive characteristics are presented for all 133 stroke cases that were identified through manually review (table 4), including 3 that could not be matched and 4 that did not involve general anesthesia (fig. 1). The majority of strokes (n = 77, 58%) occurred within the first 3 postoperative days. All patients received neuroimaging, and most received a neurology consultation during admission. Suspected etiologies varied, with embolism, large-vessel occlusion, and small-vessel occlusion all implicated, although cause was either not reported or documented as cryptogenic for 31 (23%) cases. Stroke was most common in the middle cerebral artery territory, and intravenous and endovascular interventions were uncommon. Documentation was poor at discharge, with no modified Rankin Scale documentation for 118 (89%) patients. Overall, 20 of 133 (15%) stroke

**Table 1.** Baseline Characteristics

| | All (n = 626) | Stroke (n = 126) | Controls (n = 500) | Absolute Standardized Difference |
|---|---|---|---|---|
| Age, yr, mean ± SD n = 626 | 69 ± 10 | 69 ± 11 | 69 ± 10 | 0.10 |
| Height, cm, mean ± SD n = 451 | 167 ± 12 | 165 ± 15 | 167 ± 11 | 0.16 |
| Weight, kg, mean ± SD n = 533 | 83 ± 22 | 83 ± 20 | 83 ± 22 | 0.01 |
| Body mass index, kg/m$^2$, mean ± SD n = 445 | 29 ± 7 | 30 ± 7 | 29 ± 7 | 0.08 |
| Sex, male, n (%) n = 626 | 276 (44) | 54 (43) | 222 (44) | 0.03 |
| Race, n (%) n = 625 | | | | 1.03 |
| White | 497 (79) | 67 (53) | 430 (86) | |
| Black | 72 (12) | 18 (14) | 54 (11) | |
| Asian or Pacific Islander | 8 (1.3) | 1 (0.8) | 7 (1.4) | |
| Native American | 8 (1.3) | 0 (0) | 8 (1.6) | |
| Unknown | 40 (6.4) | 40 (32) | 0 (0) | |
| ASA Physical Status, n (%) n = 626 | | | | 0.27 |
| Class I | 15 (2) | 4 (3) | 11 (2) | |
| Class II | 142 (23) | 19 (15) | 123 (25) | |
| Class III | 348 (56) | 76 (60) | 272 (54) | |
| Class IV | 118 (19) | 27 (21) | 91 (18) | |
| Class V | 3 (0.5) | 0 (0) | 3 (0.6) | |
| Comorbidities, n (%) | | | | |
| Cardiac arrhythmias | 185 (30) | 37 (29) | 148 (30) | 0.01 |
| Cardiac valvular disease | 92 (15) | 19 (15) | 73 (15) | 0.01 |
| Chronic pulmonary disease | 187 (30) | 39 (31) | 148 (30) | 0.03 |
| Coronary artery disease | 126 (22) | 31 (26) | 95 (21) | 0.12 |
| Congestive heart failure | 146 (23) | 30 (24) | 116 (23) | 0.02 |
| Diabetes | 155 (25) | 32 (25) | 123 (25) | 0.02 |
| Hypertension | 492 (79) | 100 (79) | 392 (78) | 0.02 |
| Neurologic disease | 232 (37) | 47 (37) | 185 (37) | 0.01 |
| Surgical subtype, n (%) | | | | 0.09 |
| Dentistry | 2 (0.3) | 1 (0.8) | 1 (0.2) | |
| General | 123 (20) | 29 (23) | 94 (19) | |
| Gastrointestinal radiology | 21 (3) | 4 (3) | 17 (3) | |
| Gynecologic | 29 (5) | 5 (4) | 24 (5) | |
| Interventional radiology | 11 (2) | 0 (0) | 11 (2) | |
| Nonintracranial neurosurgery | 66 (11) | 11 (9) | 55 (11) | |
| Ophthalmologic | 9 (1) | 0 (0) | 9 (2) | |
| Oral/maxillofacial | 4 (0.6) | 0 (0) | 4 (0.8) | |
| Orthopedics | 162 (26) | 27 (21) | 135 (27) | |
| Otolaryngological | 31 (5) | 5 (4) | 26 (5) | |
| Plastics | 13 (2) | 1 (0.8) | 12 (2) | |
| Thoracic | 44 (7) | 14 (11) | 30 (6) | |
| Transplant | 19 (3) | 1 (0.8) | 18 (4) | |
| Trauma | 12 (2) | 2 (1.6) | 10 (2) | |
| Urology | 56 (9) | 13 (10) | 43 (9) | |
| Vascular | 24 (4) | 13 (10) | 11 (2) | |

Surgical subtype is based on the surgical service that cared for the patient, as indicated in the Multicenter Perioperative Outcomes Group database.
ASA, American Society of Anesthesiologists.

patients died, and less than 30% of patients (39 of 133) were discharged home after the index hospitalization.

## Discussion

In this multicenter, retrospective case–control study, intraoperative hypotension and both hypo- and hypercarbia were associated with postoperative ischemic stroke. While there did not appear to be a synergistic interaction between hypotension and either hypo- or hypercarbia, they were each associated with stroke risk in an additive manner. Upon manual review of stroke cases, embolic etiologies were commonly reported, although there was no documented etiology for many cases encountered. The location of most strokes appeared to be in the middle cerebral artery territory. Therapeutic interventions (*e.g.*, endovascular thrombectomy) were uncommon, and less than 30% of stroke patients were ultimately discharged home.

It is biologically plausible that the combination of intraoperative hypotension and dyscarbia (*i.e.*, either hypocarbia or hypercarbia) could lead to ischemic stroke. Reduced cerebral blood flow, *via* hypotension and carbon dioxide dysregulation, can cause watershed infarction directly by hypoperfusion and indirectly through impaired clearance of microemboli.[36] Indeed, functional magnetic resonance

**Table 2.** Bivariable Associations

| Threshold | All n = 618 | Stroke n = 122 | Controls n = 496 | *P* Value |
|---|---|---|---|---|
| AUC MAP < 55 mmHg, mean ± SD | 5 ± 9 | 6 ± 11 | 5 ± 9 | 0.537 |
| AUC MAP < 60 mmHg, mean ± SD | 15 ± 21 | 15 ± 21 | 14 ± 21 | 0.811 |
| AUC MAP < 65 mmHg, mean ± SD | 33 ± 41 | 35 ± 38 | 33 ± 42 | 0.669 |
| AUC $ETCO_2$ ≤ 30 mmHg, mean ± SD | 6 ± 12 | 8 ± 13 | 6 ± 12 | 0.147 |
| AUC $ETCO_2$ ≤ 35 mmHg, mean ± SD | 44 ± 48 | 51 ± 51 | 42 ± 47 | 0.094 |
| AUC $ETCO_2$ ≥ 45 mmHg, mean ± SD | 9 ± 17 | 11 ± 21 | 8 ± 16 | 0.184 |

AUC, area under curve; $ETCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure.

**Table 3.** Adjusted Analysis—Seemingly Unrelated Regression Models

| Model | Equation | Threshold | Adjusted Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|---|---|
| 1* | 1 | AUC MAP < 55 mmHg | 1.10 | 1.07–1.14 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≤ 30 mmHg | 1.07 | 1.04–1.10 | < 0.0001 |
| 2 | 1 | AUC MAP < 60 mmHg | 1.04 | 1.02–1.06 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≤ 30 mmHg | 1.07 | 1.04–1.10 | < 0.0001 |
| 3 | 1 | AUC MAP < 65 mmHg | 1.02 | 1.01–1.03 | 0.001 |
| | 2 | AUC $ETCO_2$ ≤ 30 mmHg | 1.07 | 1.03–1.12 | 0.0007 |
| 4 | 1 | AUC MAP < 55 mmHg | 1.17 | 1.10–1.23 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≤ 35 mmHg | 1.02 | 1.01–1.03 | < 0.0001 |
| 5 | 1 | AUC MAP < 60 mmHg | 1.07 | 1.04–1.10 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≤ 35 mmHg | 1.02 | 1.01–1.03 | < 0.0001 |
| 6 | 1 | AUC MAP < 65 mmHg | 1.04 | 1.03–1.05 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≤ 35 mmHg | 1.03 | 1.02–1.04 | < 0.0001 |
| 7 | 1 | AUC MAP < 55 mmHg | 1.15 | 1.13–1.17 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≥ 45 mmHg | 1.10 | 1.08–1.11 | < 0.0001 |
| 8 | 1 | AUC MAP < 60 mmHg | 1.06 | 1.05–1.07 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≥ 45 mmHg | 1.10 | 1.09–1.11 | < 0.0001 |
| 9 | 1 | AUC MAP < 65 mmHg | 1.03 | 1.03–1.03 | < 0.0001 |
| | 2 | AUC $ETCO_2$ ≥ 45 mmHg | 1.11 | 1.10–1.11 | < 0.0001 |

*Primary pre-specified analysis. The adjusted odds ratios are per unit (mmHg-min) scaled to 10 units below (or outside of) each threshold. Seemingly unrelated regression models adjusted for age, sex, race (white *vs.* nonwhite), year, estimated blood loss, cardiac arrhythmia history, chronic pulmonary disease, coronary artery disease, congestive heart failure, diabetes, hypertension, neurologic disorders, and valvular heart disease.

AUC, area under the curve; $ETCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure.

imaging data in human volunteers demonstrate that the combination of reduced cerebrovascular inflow and increased cerebrovascular resistance, induced by hypocapnia, can create conditions for cerebral ischemia, particularly in those with pre-existing cerebrovascular disease.[9,18] Hyperventilation is also associated with reduced cerebral oxygenation across different surgical populations,[37–39] and low $ETCO_2$ during endovascular thrombectomy is associated with poor functional outcomes.[40] Conversely, hypoventilation and hypercapnia can also increase ischemia risk *via* the so-called "steal phenomenon," whereby cerebral blood flow is shifted away from vulnerable cerebrovascular territories where compensatory vasodilation is already maximized (*i.e.*, in the setting of atherosclerotic disease).[9] In this unselected, noncardiac surgery population, pre-pecified MAP and $ETCO_2$ thresholds demonstrated an association with postoperative ischemic stroke after adjustments for key confounders. These associations could conceivably be even stronger for patients with pre-existing cerebrovascular disease, and for the more insidious outcome of clinically silent, radiographically detected stroke,[3] but this requires testing with a prospective trial design.

Alternative explanations are also possible for the associations identified. Patients inherently at high risk for stroke may be more likely to experience intraoperative hypotension and carbon dioxide derangements. In fact, a large-scale, retrospective observational study revealed that patients with high baseline risk for stroke were more likely to experience prolonged intraoperative hypotension.[41] In this same study, there was no association between any intraoperative blood pressure threshold tested and postoperative stroke, although depth below thresholds was not tested. These findings align with a retrospective single-center study demonstrating no association between time and depth below a MAP of 70 mmHg and risk of stroke, although the median time and depth below a MAP of 70 in stroke cases could be considered mild (19 mmHg-min).[42] Conversely, a single-center retrospective study

**Table 4.** Stroke Characteristics

| | Stroke Cases (n = 133) |
|---|---|
| Age, yr, median (interquartile range) | 70 (63–77) |
| Sex, male, n (%) | 57 (43) |
| Race, n, (%) | |
| White | 71 (53) |
| Black | 19 (14) |
| Asian or Pacific Islander | 1 (0.8) |
| Unknown | 42 (32) |
| Weight, kg, mean ± SD* | 83 ± 20 |
| Body mass index, kg/m$^2$, mean (standard deviation)* | 30 (7) |
| Neuroimaging, n (%) | |
| Computed tomography only | 33 (25) |
| Magnetic resonance imaging only | 9 (7) |
| Both computed tomography and magnetic resonance imaging | 91 (68) |
| Neurology consultation, n (%) | 129 (97) |
| Postoperative day, n (%) | |
| Day of surgery | 11 (8) |
| 1 | 32 (24) |
| 2 | 17 (13) |
| 3 | 17 (13) |
| 4 | 12 (9) |
| 5–10 | 19 (14) |
| 11–15 | 12 (9) |
| 16–20 | 4 (3) |
| 21–30 | 5 (4) |
| Not reported | 4 (3) |
| Initial National Institutes of Health Stroke Scale, n (%) | |
| 1–4 | 24 (18) |
| 5–15 | 23 (17) |
| 16–20 | 5 (4) |
| ≥ 21 | 11 (8) |
| Not documented | 70 (53) |
| Etiology, n (%) | |
| Large-artery atherosclerosis | 9 (7) |
| Cardioembolic | 44 (33) |
| Embolic (noncardiac) | 28 (21) |
| Small-vessel occlusion (lacune) | 9 (7) |
| Watershed infarct | 9 (7) |
| Cryptogenic | 3 (2) |
| Other | 3 (2) |
| Not documented | 28 (21) |
| Vascular territory, n (%)† | |
| Middle cerebral artery | 64 (48) |
| Posterior cerebral artery | 32 (24) |
| Anterior cerebral artery | 13 (10) |
| Internal carotid artery | 8 (6) |
| Deep/small vessel (*e.g.*, thalamic, pontine) | 17 (13) |
| Basilar | 9 (7) |
| Vertebral | 8 (6) |
| Not specified in medical record | 22 (17) |
| Interventions, n (%) | |
| Intravenous alteplase | 8 (6) |
| Endovascular thrombectomy | 6 (5) |
| Modified Rankin Scale at discharge, n (%) | |
| 0–2 | 3 (2) |
| 3–6 | 12 (9) |
| Not documented | 118 (89) |
| Disposition, n (%) | |
| Home | 39 (29) |
| Inpatient rehabilitation facility | 32 (24) |
| Skilled nursing facility | 41 (31) |
| Hospice | 1 (0.8) |
| Death | 20 (15) |

*Weight data are available from only 103 cases, and body mass index data are available for 80 cases. Of note, the 133 cases in this table include 3 stroke cases that were unable to be matched, and 4 cases where the surgical patients underwent monitored anesthesia care (see fig. 1). †All territories affected by a given stroke are reported.

that focused on relative hypotension from preoperative baseline revealed an association between stroke and duration of time more than 30% below preoperative baseline.[43] Of note, this association was not statistically significant with duration of time more than 40% below baseline. The authors acknowledged that intraoperative hypotension could contribute to stroke risk, although other factors may play a larger role. Intraoperative derangements in blood pressure and carbon dioxide may, at the least, serve as warning signs for increased stroke risk and suggest the possible need for close postoperative monitoring.

The embolic etiologies reported in this study might further weigh against the likelihood of intraoperative malperfusion as a primary driver of stroke. Forty of the stroke cases in this series also occurred on postoperative day 5 or later. As such, thromboembolic events and hemodynamic perturbations in the postoperative period may also cause postoperative stroke. Prospective trials will be required to determine the causal relevance and effect size of these intraoperative physiologic associations with stroke, because retrospective studies are not designed to detect clinically silent stroke.[3] To provide a quantitative example of effect size from this study, 10 min with a MAP of 50 mmHg and $ETco_2$ of 28 mmHg would confer an approximate adjusted 2.02 (202%) increased relative risk of stroke based on these results (see Supplemental Digital Content 3 for calculations, http://links.lww.com/ALN/C910). These associations may be much higher for covert stroke.

Stroke characteristics and outcomes in this study are consistent with previously reported findings. The majority of strokes tend to occur within the first few days after surgery,[15,44] which may reflect hemodynamic perturbations and thromboembolic events in the early postoperative setting. Indeed, anticoagulants and antiplatelet agents are often held perioperatively, and surgical interventions induce proinflammatory and thrombotic cascades.[45] In fact, discontinuing aspirin therapy can lead to increased stroke risk for up to 4 weeks.[46] It remains unclear which patients may have high risk for such cerebrovascular thromboembolic events, although inflammatory genetic predisposition may play a role.[47] Stroke interventions were also uncommon in this study, with less than 10% of patients receiving intravenous or endovascular therapy. A previous large-scale registry study similarly demonstrated that less than 5% of identified surgical stroke patients received thrombolytic therapy.[5] Reasons for infrequent therapy are unclear but may relate to delayed stroke identification and/or guideline recommendations. In terms of the latter, it is often unrecognized that many surgeries do not represent an absolute contraindication to the use of intravenous alteplase after major surgery.[48] Thus, interventional therapy is likely underutilized, and outcomes associated with postoperative stroke tend to be quite poor. Discharges to skilled care facilities were common in our study and previous investigations.[4,5] Mortality ranges between 15 and 30%.[4,5]

This study has important limitations. As this was a retrospective analysis, causality cannot be determined from

statistical inferences generated. Many patients did not have arterial lines, precluding analysis of arterial partial pressure of carbon dioxide and $ETCO_2$ gradients. Data for certain risk factors, such as β-blockade, were not available from most sites and were not included in the analysis. Since β-blockade can reduce cerebral perfusion and oxygen delivery,[49] β-blockade may further increase stroke risk in the setting of hypotension and/or carbon dioxide dysregulation. Additionally, the confounding effects of blood pressure and $ETCO_2$ from the pre- and postoperative periods could not be determined. For example, postoperative hypotension and hypo- or hyperventilation may also lead to cerebrovascular ischemia and stroke after surgery. Additionally, biologic systems are complex, and intraoperative physiologic perturbations can synergistically interact with other factors, such as hemorrhage and cerebrovascular disease, to increase stroke risk. Thus, adjusting for these covariates may not have been appropriate given the possibility of an interaction effect. While multilevel interactions can be challenging to interpret statistically, the relationships among blood pressure, carbon dioxide, blood loss, and pre-existing cerebrovascular disease can be tested prospectively through interaction analyses and with prespecified subgroups (*i.e.*, those with and without cerebrovascular disease history). As this study was reliant on billing code data for stroke case inclusion, we were unable to test the relationship between intraoperative physiologic variables and clinically undetected stroke. Additional overt stroke cases may have been missed due to billing code error. Likewise, the sole reliance on cerebrovascular-based International Classification of Diseases billing codes may have limited the ability to detect stroke cases. In addition, these data should not be interpreted to establish an incidence of stroke given the limitations of discharge diagnosis codes for this purpose. Stroke data are also from 2015 and earlier. Temporal patterns in stroke care have since changed.[50] Last, postdischarge data were not collected for control cases. As such, the impact of hypotension, hypocarbia, or hypercarbia was not tested in relation to postdischarge outcomes.

Overall, this study demonstrated that intraoperative hypocarbia, hypercarbia, and hypotension are each independently associated with postoperative stroke. These physiologic perturbations may serve as risk factors that can be modified to reduce the incidence of postoperative stroke.

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## Competing Interests

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## Supplemental Digital Content

Supplemental Digital Content 1: STROBE and RECORD Statements, http://links.lww.com/ALN/C908
Supplemental Digital Content 2: Case Exclusions, http://links.lww.com/ALN/C909
Supplemental Digital Content 3: Total Area Under the Curve Calculations, http://links.lww.com/ALN/C910
Supplemental Digital Content 4: Interaction Testing, http://links.lww.com/ALN/C911

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