Conditioning Effect of Inhalational Anesthetics on Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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BACKGROUND: Delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (SAH) has been identified as an independent predictor of poor outcome in numerous studies.

OBJECTIVE: To investigate the potential protective role of inhalational anesthetics against angiographic vasospasm, DCI, and neurologic outcome in SAH patients.

METHODS: After Institutional Review Board approval, data were collected retrospectively for SAH patients who received general anesthesia for aneurysm repair between January 1st, 2010 and May 31st, 2018. Primary outcomes were angiographic vasospasm, DCI, and neurologic outcome as measured by modified Rankin scale at hospital discharge. Univariate and logistic regression analysis were performed to identify independent predictors of these outcomes.

RESULTS: The cohort included 390 SAH patients with an average age of 56 ± 15 (mean ± SD). Multivariate logistic regression analysis identified inhalational anesthetic only technique, Hunt-Hess grade, age, anterior circulation aneurysm and average intraoperative mean blood pressure as independent predictors of angiographic vasospasm. Inhalational anesthetic only technique and modified Fishers grade were identified as independent predictors of DCI. No impact on neurological outcome at time of discharge was noted.

CONCLUSION: Our data provide additional evidence that inhalational anesthetic conditioning in SAH patients affords protection against angiographic vasospasm and new evidence that it exerts a protective effect against DCI. When coupled with similar results from preclinical studies, our data suggest further investigation into the impact of inhalational anesthetic conditioning on SAH patients, including elucidating the most effective dosing regimen, defining the therapeutic window, determining whether a similar protective effect against early brain injury, and on long-term neurological outcome exists.

KEY WORDS: Inhalational anesthetics, Angiographic vasospasm, DCI, Clinical outcome, Aneurysmal subarachnoid hemorrhage

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Aneurysmal subarachnoid hemorrhage (SAH) accounts for approximately 5% of all the strokes[1] with extremely high morbidity and mortality. Nearly 30% of patients die[2] and 50% of survivors have long-term cognitive deficits that preclude return to work.[3] Patient's outcome after aneurysmal rupture generally depends on the initial bleeding severity and the secondary brain injury from the bleed. Secondary brain injury is divided into early brain injury (EBI),[4] which consists of blood-brain barrier breakdown, cerebral

ABBREVIATIONS: ASA, American society of anesthesiology; **CAT,** combination inhalational+intravenous anesthetic technique; **CI,** confidence interval; **DCI,** delayed cerebral ischemia; **EBI,** early brain injury; **EC-HIF-1α,** endothelial cell-derived hypoxia inducible factor-1 alpha; **ETCO2,** end-tidal carbondioxide; **ET-1,** endothelin-1; **IAT,** inhalational anesthetic technique; **ICU,** intensive care unit; **MBP,** mean blood pressure; **mRS,** modified Rankin score; **SAH,** subarachnoid hemorrhage

edema, neuroinflammation, neuronal cell death, and delayed cerebral ischemia (DCI),[5] which includes large artery vasospasm, autoregulatory dysfunction, microvessel thrombosis, and cortical spreading depression. Of the two, DCI is far more common, occurring in 30% to 40% of SAH patients.[6] The most strongly associated etiology for DCI is large artery vasospasm, though other pathophysiological factors may also contribute.[5,7] DCI is strongly associated with poor outcome and increased mortality in SAH patients.[8] Many strategies have been explored over the period of years to prevent EBI and DCI after SAH with limited effect on the morbidity and mortality of these patients. This is likely due to targeting individual elements of what has proven to be a multifactorial process.

Conditioning is a neuroprotective strategy shown to have a pleiotropic protective effect on all major cell types of central nervous system such as neurons, glial cells and vasculature.[9] In recent decades, several experimental and clinical studies have shown that certain anesthetic agents possess strong neuroprotective effect on angiographic vasospasm and DCI.[10-14] Recently in a small retrospective study,[14] we linked inhalational anesthetics exposure during aneurysm repair (coiling and clipping) to a reduced incidence of angiographic vasospasm and desflurane anesthesia in particular to a reduced incidence of DCI. The aim of the current study is to further assess the potential effect of inhalational anesthetics on angiographic vasospasm, DCI, and neurological outcome in patients with SAH in a larger patient cohort.

METHODS

This study was approved by the Institutional Review Board at our institution and did not require patient consent. Data were obtained by review of a prospectively collected database of vascular neurosurgery and neurocritical care patients and hospital charts. Patients who presented with SAH from January 1st, 2010 to May 31st, 2018 were included in this study. All patients had initial angiography for the diagnosis of aneurysms and treatment planning. Catheter or computed tomography angiography was used as a screening modality on or around day 7, if not required earlier for evaluation of DCI. Patients without evidence of an aneurysm on catheter angiogram and the patients who did not undergo a screening catheter angiogram were excluded from the study. Management of these patients was according to standard of care, and there was no specific study intervention involved. Data collected include patient demographics (age, gender, and family history), clinical presentation (Hunt-Hess grade,[15] Modified Fisher grade,[16] aneurysm characteristics (location, size), treatment characteristics (treatment modality such as surgical clipping or coiling, time between presentation and aneurysm treatment, intraprocedural perforation), anesthetic data (American society of anesthesiology [ASA] status, inhalational anesthetic technique only [IAT], intravenous anesthetic technique only, combination inhalational + intravenous anesthetic technique [CAT], sevoflurane and desflurane average end-tidal concentrations), hemodynamic and ventilatory variables (Intraoperative - average systolic blood pressure, diastolic blood pressure, mean blood pressure [MBP], heart rate, oxygen saturation, end-tidal carbondioxide [ETCO2]), comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary artery disease, liver failure, smoking history), and 3 outcome variables. Neuromonitoring for clipping/coiling is not routinely utilized in our institution, and hence the choice of anesthetic management of these patients was at the discretion of the attending anesthesiologist. The primary outcome variables assessed were angiographic vasospasm, DCI, and modified Rankin score (mRS) at discharge.

Angiographic vasospasm was defined as mild (<25% stenosis), moderate (moderate 25%-50% stenosis), or severe (>50% stenosis) narrowing of at least one major intracranial artery on a catheter angiogram.[17] If vasospasm was seen in multiple vessels, the most severely affected vessel was considered for quantification. DCI was defined as a combination of any degree of angiographic vasospasm and a decline in neurological status (either temporary or permanent) on physician examination (including alertness, orientation, cranial nerve palsy, pronator drift, or focal motor deficit) or a decrease in Glasgow Coma Scale of $\geq$2 on examination without other identifiable causes present (such as hydrocephalus, seizure, or fever). mRS (0-2) is considered as good outcome and mRS (3-6) as poor outcome for the analysis.

Statistical Analysis

Statistical analysis was performed with SPSS v. 19.0 (IBM, Armonk, New York). Univariate analysis was performed with chi square test or Fisher exact test for categorical variables, and Mann-Whitney *U* test for continuous variables. Variables that were statistically significant ($P < .05$) in the univariate analysis were entered into a forward stepwise logistic regression model, adjusting for the relevant clinical variables. A model parameter with $P < .05$ was considered statistically significant.

RESULTS

A total of 436 patients with the diagnosis of aneurysmal SAH were identified. Of these, 24 did not receive screening catheter angiography to assess for cerebral vasospasm for a variety of reasons, data for 22 patients could not be retrieved, so a total of 390 patients (115 males, 276 females) with a mean age of 56 $\pm$ 15 (Mean $\pm$ SD) were ultimately included. Aneurysms were located in the anterior circulation in 326 patients (84%) and in the posterior circulation in 64 patients (16%). Surgical clipping was performed in 151 patients (39%), and endovascular coiling was performed in 239 patients (61%). IAT (isoflurane, sevoflurane, or desflurane) was employed in 298 (76%) patients, while a CAT (sevoflurane or desflurane plus propofol) was employed in 84 (22%) patients. Of the 390 SAH patients, 236 (61%) developed angiographic vasospasm, 114 (29%) developed DCI. Out of 390 patients, mRS data was unavailable for 20 patients. Of the 370 patients with available mRS data, 169 (46%) had good outcome at time of hospital discharge.

Angiographic Vasospasm

Tables 1 and 2 show the univariate analysis comparison in patients with and without angiographic vasospasm. Significant differences were found for the following variables: patient age, Hunt-Hess grade, Modified Fisher grade, aneurysm treatment type, aneurysm location, anesthetic technique, average intraoperative MBP, oxygen saturation, ETCO2, and length of stay in the hospital and intensive care unit (ICU). Table 3 shows the logistic regression performed to identify factors independently associated

TABLE 1. Clinical and Aneurysm Characteristics by Angiographic Vasospasm Outcome

Characteristic	No angiographic vasospasm (n = 154)	Yes angiographic vasospasm (n = 236)	*P* value
Age (Median/IQR)	58/22 (48, 70)	54/16 (47, 63)	.014
Male gender n (%)	50 (33%)	65 (28%)	.166
Family history n (%)	11 (7%)	18 (8%)	.887
Anterior circulation n (%)	121 (79%)	205 (87%)	.031
Clipping n (%)	45 (29%)	106 (45%)	.002
Time of rupture to coiling or clipping (median/IQR)	1/1 (1, 2)	1/0 (1, 1)	.091
H and H grading (median/IQR)	2/1 (2, 3)	3/2 (2, 4)	<.0001
Modified Fisher (median/IQR)	3/3 (1, 4)	3/2 (2, 4)	.001
Size of ruptured aneurysm (median/IQR)	6/4 (4, 8)	5/4 (4, 8)	.749
Perforation n (%)	10 (7%)	17 (7%)	.766
ICU length of stay (median/IQR)	10/8 (6, 14)	16/10 (11, 21)	<.0001
Total hospital length of stay (median/IQR)	13/10 (9, 19)	19/12 (14, 26)	<.0001
COPD n (%)	15 (10%)	17 (7%)	.372
Smoking n (%)	51 (33%)	83 (35%)	.677
HTN n (%)	93 (60%)	132 (60%)	.222
Diabetes n (%)	23 (15%)	24 (10%)	.106
CAD n (%)	15 (10%)	17 (7%)	.115
Liver Failure n (%)	1 (1%)	2 (1%)	.656

Categorical variables are represented as number (percent). Continuous variables are presented as presented as median/IQR. $P < .05$ is statistically significant.
BMI = body mass index; H and H = Hunt and Hess grading; COPD = chronic obstructive pulmonary disorder; TIA = transient ischemic attack; OSA = obstructive sleep apnea; HTN = hypertension; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease.

TABLE 2. Anesthetic and Hemodynamic Characteristics by Angiographic Vasospasm Outcome

Characteristic	No angiographic vasospasm (n = 154)	Yes angiographic vasospasm (n = 236)	*P* value
ASA status (median/IQR)	3/1 (3, 4)	3/1 (3, 4)	.27
Propofol n (%)	23 (15%)	68 (29%)	.002
Desflurane n (%)	57 (37%)	68 (29%)	.09
Inhalational anesthetics only n (%)	131 (85%)	167 (71%)	.001
Combined inhalational/intravenous anesthetic n (%)	19 (12%)	65 (28%)	<.0001
TIVA only n (%)	4 (3%)	4 (2%)	.539
Sevoflurane average end-tidal concentration (median/IQR)	1.48/0.57 (1.15, 1.72)	1.44/0.55 (1.12, 1.67)	.472
Desflurane average end-tidal concentration (median/IQR)	5.14/1.14 (4.64, 5.78)	4.69/1.04 (4.27, 5.31)	.035
Average SBP (median/IQR)	120/19 (110, 129)	121/16 (113, 128)	.491
Average DBP (median/IQR)	62/13 (57, 70)	64/12 (59, 70)	.151
Average MBP (median/IQR)	80/11 (74, 86)	82/11 (77, 88)	.02
Average HR (median/IQR)	73/15 (65, 80)	74/15 (67,82)	.077
Average SPO2 (median/IQR)	99/2 (98, 100)	99/1 (99, 100)	.029
Average ETCO2 (median/IQR)	32/5 (29, 34)	31/5 (28, 33)	.014

Categorical variables are represented as number (percent). Continuous variables are presented as median/IQR. $P < .05$ is statistically significant for all comparisons.
ASA = American society of Anesthesiology; TIVA = total intravenous anesthesia; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; HR = heart rate; SPO2 = oxygen saturation; ETCO2 = end tidal carbon dioxide.

with angiographic vasospasm. Independent risk factors for angiographic vasospasm included (1) IAT, (2) Hunt-Hess grade, (3) age, (4) anterior circulation aneurysm, and (5) average intraoperative MBP.

DCI

Tables 4 and 5 show the univariate analysis comparison in patients with and without DCI. Significant differences were found for the following variables: treatment type, Hunt-Hess

TABLE 3. Results of Logistic Regression Analysis for Predictors of ANY Angiographic Vasospasm After SAH, Using the Stepwise Forward Method

Characteristic	Odds ratio	95% CI	*P* value
Age at SAH	0.979	0.963-0.995	.010
Hunt and Hess	2.180	1.633-2.910	<.0001
Inhalational anesthetics only (0 = n, 1 = y) (1)	0.405	0.222-0.738	.003
Location of ruptured aneurysm (anterior = 1, posterior = 2) (1)	0.359	0.182-0.708	.003
Average MBP	1.032	1.006-1.058	.015

Values are represented as odds ratio with 95% CI. $P < .05$ is statistically significant.

TABLE 4. Clinical and Aneurysm Characteristics by DCI Outcome

Characteristic	No DCI (n = 276)	Yes DCI (n = 114)	*P* value
Age (median/IQR)	55/20 (47, 67)	54/16 (48, 64)	.653
Male gender n (%)	79 (29%)	36 (32%)	.575
Family history n (%)	22 (8%)	7 (6%)	.510
Anterior circulation n (%)	229 (83%)	97 (85%)	.608
Clipping n (%)	98 (36%)	53 (46%)	.046
H and H grading (median/IQR)	3/1 (2, 3)	3/2 (2, 4)	<.0001
Modified Fisher (median/IQR)	3/3 (1, 4)	3/1 (3, 4)	<.0001
Size of the ruptured aneurysm (Median/IQR)	5/4 (4, 8)	6/4 (4, 8)	.981
Time of rupture to coiling or clipping (median/IQR)	1/1 (1, 2)	1/1 (1, 2)	.887
Length of stay in ICU (Median/IQR)	11/8 (8, 16)	18/9 (14, 23)	<.0001
Total hospital length of stay (median/IQR)	14/9 (11, 20)	24/12 (17, 29)	<.0001
Perforation n (%)	23 (8%)	4 (3.6%)	.095
COPD n (%)	26 (9%)	6 (5%)	.174
HTN n (%)	167 (61%)	58 (51%)	.08
Diabetes n (%)	36 (13%)	11 (10%)	.349
CAD n (%)	22 (8%)	7 (6%)	.531
Liver failure n (%)	3 (1%)	0 (0%)	.353
Smoking n (%)	91 (33%)	43 (38%)	.369

Categorical variables are presented as number (percent). Continuous variables are presented as median/IQR. $P < .05$ is statistically significant.
BMI = body mass index; H and H = Hunt and Hess grading; COPD = chronic obstructive pulmonary disorder; TIA = transient ischemic attack; OSA = obstructive sleep apnea; HTN = hypertension; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease.

grade, Modified Fisher grade, type of anesthetic used, mRS score at discharge, and length of stay in the hospital and ICU. Table 6 shows the logistic regression performed to identify factors independently associated with DCI. IAT and Modified Fisher grade are identified as significant predictors of DCI.

Clinical Outcome

Clinical outcome was analyzed using mRS score at discharge. Tables 7 and 8 show the univariate analysis comparison in patients with good and poor outcomes. Significant differences were found for the following variables: age, Hunt-Hess grade, Modified Fisher grade, hypertension, ASA status, type of anesthetic used, and length of stay in the hospital and ICU. Table 9 shows the logistic regression performed to identify factors independently associated with poor outcomes mRS (3-6). (1) Modified Fisher grade, (2) age, and (3) patient's ASA status are identified as significant predictors of poor outcomes mRS (3-6).

DISCUSSION

The key results in our study are as follows: (1) Hunt-Hess grade, IAT, anterior circulation aneurysm location, patient age, and intraoperative average MBP were identified as independent risk factors for angiographic vasospasm following SAH; (2) Modified Fisher grade and IAT were identified as independent predictors for DCI following SAH; and (3) Modified Fisher grade, patient age, and ASA status were identified as independent risk factors for neurologic outcomes at hospital discharge following SAH. The most novel of these results is the identification that use of an IAT for general anesthesia during aneurysm repair is

TABLE 5. Anesthetic and Hemodynamic Characteristics by DCI Outcome

Characteristic	No DCI (n = 276)	Yes DCI (n = 114)	*P* value
ASA status (Median/IQR)	3/1 (3, 4)	3/1 (3, 4)	.130
Inhalational anesthetics only n (%)	219 (79%)	79 (69%)	.033
Desflurane n (%)	94 (34%)	31 (27%)	.186
Propofol n (%)	56 (21%)	35 (31%)	.027
Combined inhalational/intravenous anesthetic n (%)	50 (18%)	34 (30%)	.011
TIVA only n (%)	7 (3%)	1 (1%)	.268
Sevoflurane average end-tidal concentration (Median/IQR)	1.44/0.52 (1.15, 1.67)	1.44/0.61 (1.08, 1.69)	.654
Desflurane average end-tidal concentration (Median/IQR)	5.14/1.12 (4.58, 5.7)	4.47/1.24 (3.45, 4.69)	<.0001
Average SBP (median/IQR)	120/18 (111, 129)	119/14 (114, 127)	.810
Average DBP (median/IQR)	64/14 (57, 71)	63/10 (58, 68)	.772
Average MBP (median/IQR)	81/12 (75, 88)	82/9 (77, 85)	.537
Average HR (median/IQR)	73/15 (66, 81)	74/16 (66, 82)	.419
Average SPO2 (median/IQR)	99/2 (98, 100)	99/1 (99, 100)	.748
Average ETCO2 (median/IQR)	31/5 (29, 33)	31/6 (28, 33)	.090

Categorical variables are represented as number (percent). Continuous variables are represented as (Mean ± SD). Variables which are not normally distributed are presented as median and IQR (25%-75%). $P < .05$ is statistically significant.
ASA = American society of Anesthesiology; TIVA = total intravenous anesthesia; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; HR = heart rate; SPO2 = oxygen saturation; ETCO2 = end tidal carbon dioxide.

TABLE 6. Results of Logistic Regression Analysis for Predictors of DCI After SAH, Using the Stepwise Forward Method

Characteristic	Odds ratio	95% CI	*P* value
Modified Fisher	1.882	1.504-2.354	<.0001
Inhalational anesthetics only (0 = n, 1 = y)	0.507	0.297-0.864	.013

Values are represented as odds ratio with 95% CI. $P < .05$ is statistically significant.

an independent predictor of less angiographic vasospasm and less DCI in SAH patients. This is an extension of our previous study where we examined a smaller cohort of SAH patients and showed that IAT is associated with less angiographic vasospasm.[15] In combination, these two studies provide important clinical validation of preclinical data that showed anesthetic conditioning provides powerful protection against multiple components of DCI leading to improved neurological outcome following experimental SAH.[11]

Importantly, our study does not show a statistically significant effect of IAT on patient outcome as assessed by mRS at time of hospital discharge. This result has several possible explanations: (1) Timing of exposure of anesthetics: Preclinical evidence by Milner et al[11] showed that isoflurane conditioning initiated 6 h after SAH induction does not result in neurovascular protection while isoflurane conditioning initiated up to 3 h after SAH provided significant neurovascular protection. This indicates that a therapeutic window for the neurological protection afforded by anesthetics is present. It is therefore possible that SAH patients in our study group were not exposed to IAT within an optimal time period to achieve maximal neurological protection. (2) Dose and/or duration of inhalational anesthetics: It is possible that our SAH patients were not exposed to the necessary dose and/or duration of inhalational anesthetics to achieve maximal neurological protection. This is supported by a recent experimental study[18] where varying doses (1.5%, 3%, and 4.5%) and durations (30, 60, and 90 min) of sevoflurane conditioning in experimental SAH were examined and anesthetic parameters that optimized the degree of neurologic protection were identified (1.5% and 3% sevoflurane exposure for up to 60 min). (3) Differential impact of inhalational anesthetic types: Interestingly, in the univariate analysis, we noted that greater exposure to desflurane anesthetic (as measured by average end-tidal concentration) was associated with less angiographic vasospasm, less DCI, and better neurologic outcome at hospital discharge, though it was not significant in multivariate analysis. It is therefore possible that certain inhalational anesthetics provide greater neurovascular protection than others. This notion is supported by studies where desflurane (as compared to propofol) was associated with lower transcranial doppler evident vasospasm[13] and reduced endothelin-1 (ET-1) plasma levels during aneurysm surgery.[10] (4) Impact of rescue therapy: It is possible that rescue therapies such as hemodynamic augmentation and intravascular interventions instituted in our cohort of SAH patients suffering DCI may have negated the potential positive impact of inhalational anesthetics on neurological outcome.

Inhalational Anesthetics and EBI

The beneficial effects of inhalational anesthetic conditioning have also been extended to EBI—another important driver of secondary brain injury after SAH. In an elegant series of

TABLE 7. Clinical and Aneurysm Characteristics by mRS Good vs Poor Outcome

Characteristic	mRS good outcome (n = 169)	mRS poor outcome (n = 202)	*P* value
Age (median/IQR)	50/15 (44, 59)	60/22 (50, 71)	<.0001
Male gender n (%)	43 (25%)	63 (31%)	.211
Family history n (%)	18 (11%)	11 (6%)	.055
Anterior circulation n (%)	139 (82%)	170 (85%)	.623
Clipping n (%)	70 (41%)	72 (36%)	.270
H and H grading (median/IQR)	2/1 (2, 3)	3/2 (2, 4)	<.0001
Modified Fisher (median/IQR)	2/2 (1, 3)	3/2 (2, 4)	<.0001
Size of the ruptured aneurysm (median/IQR)	5/3 (4, 7)	6/4 (4, 8)	.322
Time of rupture to coiling or clipping (median/IQR)	1/1 (1, 2)	1/1 (1, 2)	.217
Length of stay in ICU (median/IQR)	11/8 (7, 15)	15/12 (10,22)	<.0001
Total hospital length of stay (median/IQR)	14/8 (10, 18)	20/14 (14, 28)	<.0001
Perforation n (%)	13 (8%)	14 (7%)	.729
COPD n (%)	11 (7%)	20 (10%)	.240
HTN n (%)	85 (50%)	130 (65%)	.006
Diabetes n (%)	15 (9%)	29 (14%)	.104
CAD n (%)	13 (8%)	14 (7%)	.779
Liver failure n (%)	0 (0%)	3 (1%)	.112

Categorical variables are represented as number (percent). Continuous variables are represented as (Mean ± SD). Variables which are not normally distributed are presented as median and IQR (25%-75%). $P < .05$ is statistically significant.
BMI = body mass index; H and H = Hunt and Hess grading; COPD = chronic obstructive pulmonary disorder; TIA = transient ischemic attack; OSA = obstructive sleep apnea; HTN = hypertension; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease.

TABLE 8. Anesthetic and Hemodynamic Characteristics by mRS Good vs Poor Outcome

Characteristic	mRS good outcome (n = 169)	mRS poor outcome (n = 202)	*P* value
ASA status (Median/IQR)	3/1 (3, 4)	3/1 (3, 4)	<.0001
Inhalational anesthetics only n (%)	133 (79%)	152 (75%)	.433
Combined inhalational/intravenous anesthesia n (%)	22 (14%)	47 (23%)	.310
TIVA only n (%)	4 (2%)	3 (1%)	.534
Sevoflurane Average end-tidal concentration (median/IQR)	1.52/0.48 (1.2, 1.68)	1.41/0.56 (1.11, 1.67)	.105
Desflurane Average end-tidal concentration (median/IQR)	5.17/1.19 (4.58, 5.77)	4.72/1.45 (3.91, 5.31)	.002
Average SBP (median/IQR)	119/19 (109, 128)	121/17 (113, 130)	.051
Average DBP (median/IQR)	64/11 (59, 71)	63/13 (57, 70)	.128
Average MBP (median/IQR)	82/12 (76, 87)	80/12 (76, 87)	.86
Average HR (median/IQR)	73/13 (66, 79)	74/17 (66,83)	.361
Average SPO2 (median/IQR)	99/1 (98, 100)	99/2 (98, 100)	.516
Average ETCO2 (median/IQR)	31/5 (28, 33)	31/4 (29, 33)	.933

Categorical variables are represented as number (percent). Continuous variables are represented as (Mean ± SD). Variables which are not normally distributed are presented as median and IQR (25%-75%). $P < .05$ is statistically significant.
ASA = American society of Anesthesiology; TIVA = total intravenous anesthesia; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; HR = heart rate; SPO2 = oxygen saturation; ETCO2 = end tidal carbon dioxide.

experiments utilizing an endovascular perforation mouse model of SAH, Zhang and colleagues showed that isoflurane conditioning significantly protects against multiple components of EBI including improved neurological outcome at 24h.[19-21] Similar protection against SAH-induced EBI has been shown for another inhalational anesthetic, sevoflurane, by a separate laboratory.[18] If these observations were validated in future clinical studies, it would suggest that anesthetic conditioning has the exciting potential to provide additive or even synergistic protective effects against EBI and DCI in SAH patients and would set the necessary foundation for future prospective clinical trials designed to assess the impact of inhalational anesthetic conditioning on EBI, DCI, and long-term neurological outcome in SAH patients.

TABLE 9. Results of Logistic Regression Analysis for Predictors of mRS Outcome After SAH, Using the Stepwise Forward Method

Characteristic	Odds ratio	95% CI	*P* value
Age at SAH	1.042	1.024-1.060	<.0001
Modified Fisher	1.365	1.129-1.649	.001
ASA status	1.650	1.189-2.290	.003

Values are represented as odds ratios with 95% CI. $P < .05$ is statistically significant.
ASA = American society of Anesthesiology.

Inhalational Anesthetics and Neuromonitoring

Though intravenous agents are commonly used to achieve burst suppression by electroencephalography as a means to reduce risk of ischemic brain injury during aneurysm surgery, it can be also be achieved by inhalational anesthetic agents. On the other hand, inhalational anesthetic agents are known to significantly affect somatosensory and motor evoked potentials, while intravenous agents like propofol do not.[22] Therefore, the potential benefits of an IAT on incidence or severity of DCI would need to be balanced against the potential benefits of intraoperative neuromonitoring.

Potential Mechanisms of Inhalational Anesthetic-Induced Cerebral Vessel Protection

At least 2 molecular mechanisms underlying the protective effect of inhalational anesthetics on SAH-induced vasospasm and DCI have been identified. First, Milner et al[11] found in an endovascular perforation mouse model of SAH that isoflurane conditioning produced robust multifaceted protection against SAH-induced DCI, and that this protection was mediated via an *increase* in endothelial cell-derived hypoxia inducible factor-1 alpha (EC-HIF-1α). HIF-1α is a transcription factor that regulates multiple target genes, several of which have well described roles in cerebral vessel function including endothelial nitric oxide synthase, inducible nitric oxide synthase, and vascular endothelial growth factor.[23,24] In contrast, propofol anesthesia has been shown to *decrease* HIF-1α levels.[25] Second, 2 studies have linked the potent vasoconstrictor, ET-1, to inhalational anesthetic-induced cerebral vessel protection. Experimentally, Park et al[26] showed that isoflurane exposure (0-2 minimum alveolar concentration) led to attenuation of ET-1-induced vasoconstriction of cortical microvessels harvested from mice previously subjected to SAH via cisterna magna injection. Clinically, Wang et al[10] noted that SAH patients anesthetized with desflurane for aneurysm surgery experienced a significant *decline* in intraoperative ET-1 levels as compared to preinduction. In contrast, Luo et al[27] noted that SAH patients undergoing propofol anesthesia during aneurysmal surgery had *no impact* on intraoperative ET-1 levels.

In total, results from the present study provide the most compelling evidence to date that inhalational anesthetics may afford protection against angiographic vasospasm and DCI in SAH patients. This finding has two important implications. First, it suggests that use of an IAT for general anesthesia during aneurysm repair reduces the incidence of angiographic vasospasm and DCI in SAH patients. If validated in separate patient cohorts and/or a prospective clinical trial, this would have direct implications on the choice of anesthetic technique in SAH patients undergoing aneurysm repair. Second, it suggests that anesthetic conditioning (or molecular therapies designed to mimic the protection provided by inhalational anesthetics) could be developed as a stand-alone therapeutic strategy as a means for reducing secondary brain injury and improving neurological outcome in SAH patients. Therefore, additional preclinical and clinical studies investigating the impact and underlying mechanisms of inhalational anesthetic conditioning on SAH-induced brain injury and neurological deficits are therefore warranted.

Limitations of the Study

Our study has several limitations: (1) Our sample size remains relatively small, so it may be underpowered to evaluate the association between inhalational anesthetics and neurological outcome after SAH; (2) our study design is a single center retrospective analysis that has its own inherent limitations; (3) our study did not specifically evaluate the impact of inhalational anesthetics on EBI; (4) lack of a standard protocol regarding choice of anesthetic technique (IAT vs CAT) raises the potential risk of confounding our results; and (5) our patient cohort had insufficient patient number to directly examine the impact of IAT vs intravenous only anesthetic technique.

CONCLUSION

Our study provides important clinical evidence that an association between inhalational anesthetic conditioning and protection against angiographic vasospasm and DCI exists. Though our findings are preliminary and need validation in separate patient cohorts and utilizing prospective study design, they support the growing body of evidence that inhalational anesthetic conditioning represents as a novel therapeutic approach for ameliorating and/or preventing secondary brain injury and improving long-term neurological outcome in patients with aneurysmal SAH.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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