Stroke and Intraoperative Hypotension: To Sleep, Perchance to Stroke—Ay, There's the Rub

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The article by Hsieh et al in this month's issue of *Anesthesia and Analgesia* is not the first to suggest that there is not a strong correlation between intraoperative hypotension and postoperative "stroke" (used herein to refer to focal or global ischemic cerebral injury not related to intracerebral or subarachnoid hemorrhage).[1–3] Hsieh et al reviewed the electronic medical records of patients at the Cleveland Clinic to identify those in whom strokes, as identified by the *International Classification of Diseases*, Ninth Revision, codes, had occurred in the postoperative period after nonneurologic, noncardiac, noncarotid surgery. They then examined electronic anesthesia records to extract an area under the curve metric of hypotension, combining duration and degree of mean arterial pressure (MAP) reduction below MAP thresholds of 70, 65, and 60 mm Hg. They propensity-matched 4 nonstroke patients with each of those who had sustained a stroke. They report, "Stroke patients did not experience a greater degree of hypotension than controls"; and they conclude, "There was no association between stroke and intraoperative hypotension." One hundred four patients (0.11%), of 97,304 with complete data, sustained strokes. Seventeen of those strokes were evident on the day of surgery. The authors note that there is a prothrombotic state that prevails in the postoperative period that may have contributed to the occurrence of the 87 delayed strokes. Ergo, of the limited number of strokes that they identified, many if not most are probably not an immediate consequence of intraoperative hemodynamic management. Ergo, the number of strokes on which this comparison is based is (fortunately) very small, that is, 17.

This editorial commentary is intended to address 2 questions and offer 2 conclusions: (1) Does what we already know about normal cerebral physiology make the observations of Hsieh et al surprising? Absolutely not. (2) Should the present communication make us even more casual about intraoperative hypotension than already appears (to this observer) to be the case? Absolutely not.

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First, to the matter of normal physiology. The primary definition of "hypotension" used by Hsieh et al was an MAP of less than 70 mm Hg. However, as most of you sit at your desks reading this commentary, the MAP at your circle of Willis is about 70 mm Hg. Were you to be anesthetized in the supine position, an MAP of 70 mm Hg is a normal MAP for at least your cerebrum. Ischemic symptoms do not begin to appear in awake subjects until MAPs reach 40 to 50 mmHg at the circle of Willis.[4,5] Even at that threshold, the relative ischemia is not immediately injurious, and probably not injurious at all if MAP does not fall below that threshold.

Why should hypotension cause cerebral injury in the first place? The phenomenon of cerebral blood flow autoregulation maintains CBF across some range of MAPs. However, there is probably much more inherent variability in a normal population than is implied by standard text book diagrams (see Willie et al,[6] Joshi et al,[7] and Drummond[8]). Furthermore, the average lower limit of autoregulation, that is, the MAP below which CBF becomes pressure passive and falls pari passu with declining MAP, is likely to be an MAP much greater than the once prevalent and still reputably cited[9] value of 50 mm Hg. One way or another, in all of us CBF eventually becomes pressure passive and decreases as MAP declines. The threshold for ischemic symptoms (which is not synonymous with the threshold for injury) is a CBF reduction of about 40%.[4,5] In volunteer studies, that threshold is reached, as noted previously, at average MAPs of 40 to 50 mm Hg. In one clinical investigation, at MAPs of 50 mm Hg, many sedated, initially normotensive subjects were close to but did not exceed that 40% threshold.[10] It should therefore not be surprising therefore that the MAPs observed by Hsieh were not associated with stroke. You can get away with a lot; however, the phenomenon of watershed or boundary zone ischemia[11] has taught us that somewhere there is a limit to central nervous system tolerance.[a] That limit is likely to occur, in most normal adults, at values less than 50 mm Hg.

The other mechanisms by which hypotension might contribute to stroke are largely speculation, albeit reasonable speculation. Surgery is trauma, carefully choreographed trauma to be sure, but trauma nonetheless. Trauma yields a procoagulant state. It is possible that circumstances of low, but nutritively adequate, flow nonetheless result in relative

[a]The "watershed" concept was originally named the "Letzte Wiese" (German: Last Meadow) phenomenon.[12] The latter seems a better metaphor. When the water pressure falls, it is the last field in the distribution system that turns brown. Water drains away from watersheds, not toward them.

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stasis and thereby predispose to spontaneous thrombosis, especially in already diseased vessels. I do not believe that the reality of this phenomenon has actually been confirmed but it seems feasible.[b] Most non-watershed strokes, however, are nonetheless probably embolic. Therein lies a second potential contribution of hypotension to stroke. If embolization occurs, as previously suggested,[13] might there be a lesser likelihood of mechanical clearance during periods of low perfusion pressure, or might poorer collateral flow while native clot-clearing mechanisms operate aggravate the final outcome? Here, for illustration, I will turn to anecdote. A sexagenarian physician friend recently found himself with sufficiently severe spine disease to agree to a lumbar instrumentation. In the preoperative holding area, before any intervention, he abruptly became aphasic. Examination revealed profound right-sided sensory deficits. A stroke code and thrombolysis ensued. He is now normal. Would that be the case if his spontaneous event had occurred 20 minutes later, at the beginning of 4 or more hours of relative hypotension? (I know. That ignores the issue of no longer being a thrombolysis candidate. But you grasp the point.)

The second question posed at the outset was, should we be reassured by the report of Hsieh et al that there is a nonrelationship, or at worst a very weak one, between intraoperative hypotension and stroke? I doubt it. The number of strokes that actually occurred was very low and that may well be because the data indicate that, at the Cleveland Clinic, blood pressure control is rather more careful than I perceive it to be across the broad spectrum of North American institutions. Figure 4 and Supplemental Figures 1 and 2 indicate that there is really not much hypotension during anesthesia at that institution. I have had that impression before. In a 2012 publication (about a clinical study of intraocular pressure during spine fusion surgery), I was struck by reported average intraoperative MAPs in excess of 80 mm Hg.[14] I doubt that that is the North American norm, either then or now. I would entrust my cerebral well-being to these clinicians. But, I am forced to doubt that the circumstances of the present study provide an opportunity for a realistic confirmation of a nonrelationship between intraoperative hypotension and stroke, and certainly not a nonrelationship between hypotension and stroke severity.

I believe that all the mechanisms just discussed (reduced collateral flow, reduced clearance of emboli, stasis) are sufficiently reasonable speculation that they should encourage the avoidance of hypotension that is not necessary for the safe conduct of a surgical procedure. I think that it is reasonable to suspect that even if it requires very significant hypotension to cause stroke in healthy subjects whose nervous systems are not otherwise under threat, strokes that occur spontaneously during anesthesia will be aggravated by sustained hypotension. Until someone proves otherwise, I think that that should be the working assumption and it should influence decisions and encourage caution about intraoperative blood pressure management, at a minimum in individuals perceived to be at increased risk for stroke. ■

[b]One will find assertions in the literature as to the frequent occurrence of thrombotic stroke. But, I will argue that this is the intellectually sloppy phenomenon of one reviewer's speculation becoming the next reviewer's fact.

DISCLOSURE

Name: John C. Drummond MD, FRCPC.
Contribution: This author wrote the manuscript.
This manuscript was handled by: Gregory Crosby, MD.

REFERENCES

1. Hsieh JK, Kletsas D, Clunn G, Hughes AD, Schachter M, Demoliou-Mason C. p53, p21(WAF1/CIP1), and MDM2 involvement in the proliferation and apoptosis in an in vitro model of conditionally immortalized human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2000;20:973–981.
2. Hart R, Hindman B. Mechanisms of perioperative cerebral infarction. *Stroke*. 1982;13:766–773.
3. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology*. 2012;116:658–664.
4. Finnerty FA Jr, Witkin L, Fazekas JF. Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. *J Clin Invest*. 1954;33:1227–1232.
5. Njemanze PC. Critical limits of pressure-flow relation in the human brain. *Stroke*. 1992;23:1743–1747.
6. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol*. 2014;592:841–859.
7. Joshi B, Ono M, Brown C, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg*. 2012;114:503–510.
8. Drummond JC. The lower limit of autoregulation: time to revise our thinking? *Anesthesiology* 1997;86:1431–1433.
9. Russell JA. Is there a good MAP for septic shock? *N Engl J Med*. 2014;370:1649–1651.
10. Bombardieri AM, Sharrock NE, Ma Y, Go G, Drummond JC. An observational study of cerebral blood flow velocity during hypotensive epidural anesthesia. *Anesth Analg*. 2016;122:226–233.
11. Momjian-Mayor I, Baron JC. The pathophysiology of watershed infarction in internal carotid artery disease: review of cerebral perfusion studies. *Stroke*. 2005;36:567–577.
12. Hossmann KA, Heiss WD. History of the Letzte Wiese/last meadow concept of brain ischemia. *Stroke*. 2016;47:e46–e50.
13. Bijker JB, Gelb AW. Review article: the role of hypotension in perioperative stroke. *Can J Anaesth*. 2013;60:159–67.
14. Farag E, Sessler DI, Kovaci B, et al. Effects of crystalloid versus colloid and the α-2 agonist brimonidine versus placebo on intraocular pressure during prone spine surgery: a factorial randomized trial. *Anesthesiology*. 2012;116:807–815.

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The Association Between Mild Intraoperative Hypotension and Stroke in General Surgery Patients

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BACKGROUND: Intraoperative hypotension may contribute to perioperative strokes. We therefore tested the hypothesis that intraoperative hypotension is associated with perioperative stroke.
METHODS: After institutional review board approval for this case-control study, we identified patients who had nonneurological, noncardiac, and noncarotid surgery under general anesthesia at the Cleveland Clinic between 2005 and 2011 and experienced a postoperative stroke. Control patients not experiencing postoperative stroke were matched in a 4-to-1 ratio using propensity scores and restriction to the same procedure type as stroke patients. The association between intraoperative hypotension, measured as time-integrated area under a mean arterial pressure (MAP) of 70 mm Hg, and postoperative stroke was assessed using zero-inflated negative binomial regression.
RESULTS: Among 106 337 patients meeting inclusion criteria, we identified 120 who had confirmed postoperative stroke events based on manual chart review. Four-to-one propensity matching yielded a final matched sample of 104 stroke cases and 398 controls. There was no association between stroke and intraoperative hypotension. Stroke patients were not more likely than controls to have been hypotensive (odds ratio, 0.49 [0.18–1.38]), and among patients with intraoperative hypotension, stroke patients did not experience a greater degree of hypotension than controls (ratio of geometric means, 1.07 [0.76–1.53]).
CONCLUSIONS: In our propensity score–matched case-control study, we did not find an association between intraoperative hypotension, defined as MAP < 70 mm Hg, and postoperative stroke. (Anesth Analg 2016;123:933–9)

Perioperative stroke is a devastating complication of surgery, with an apparent incidence of approximately 0.1% in noncardiac, nonneurological surgery (general surgery).[1] Although commonly defined (as well as by American College of Surgeons National Surgical Quality Improvement Program) as occurring within 30 days after surgery,[1,2] most perioperative strokes occur postoperatively (rather than intraoperatively) with the majority occurring within 7 days.[3,4] In contrast to strokes in the general population, which have a mortality rate of 12.6%, strokes during or after general surgery have a mortality rate that ranges from 26% to as high as 87% in patients who have had a previous stroke.[2,5]

The incidence of perioperative stroke varies according to the nature and complexity of the surgical procedure, in addition to other factors such as advanced age, sex, and comorbidities.[5,6] Perioperative strokes are most common in patients having cardiac, neurological, and carotid artery surgery.[7] For instance, the rate of perioperative stroke in cardiac surgery ranges from 1.9% to 9.7% depending on the complexity of the surgery,[7–9] whereas, in general surgery, the risk is considerably lower.[1,7,10,11] The pathophysiology of perioperative stroke tends to be ischemic rather than hemorrhagic. In cardiac surgery, strokes are mainly embolic, whereas strokes in general surgery tend to be thrombotic.[7] It is unclear why general surgery is associated with thrombotic strokes; however, factors such as endothelial dysfunction and surgically induced hypercoagulability—both of which may persist for days after surgery—may play a role.[2]

Recently, hypotension has regained interest as a potential risk factor for perioperative stroke. The Perioperative Ischemic Evaluation Study (POISE) trial, completed in 2007, found an increased rate of death in patients receiving metoprolol versus placebo for noncardiac surgery. Increased mortality was associated with a higher rate of postoperative stroke, for which clinically important hypotension had the largest attributable risk.[12] However, the contribution of intraoperative versus postoperative hypotension, and hypotension in general, to perioperative stroke remains unclear. A recent study by Bijker et al,[13] for example, reported that the duration of time that mean arterial pressure (MAP) was decreased >30% from baseline was significantly associated with postoperative stroke. In contrast, several older studies identified no relationship between intraoperative hypotension and stroke, while maintaining that postoperative hypotension may contribute.[3,10,14]

We therefore tested the hypothesis that intraoperative hypotension is associated with perioperative stroke. Specifically, we evaluated (1) whether patients with postoperative stroke were more likely to become hypotensive (as defined by MAP < 70 mm Hg at any point during surgery) and (2) whether hypotensive events in stroke patients were more severe than in patients without stroke.

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METHODS

The study was approved by the institutional review board, which waived the requirement for individual consent. From the Cleveland Clinic Perioperative Health Documentation System registry, we obtained data on 106 337 adult, American Society of Anesthesiologists Physical Status I–IV patients who had elective noncardiac, nonneurological, and noncarotid surgery with general anesthesia at Cleveland Clinic between January 2005 and December 2011. This was the maximum number of patients available to us at the time of study design. Only the most recent visit per patient was included, and the index surgery within a given visit was the first in which there was an anesthesia record. A patient flow diagram for our study is given in Figure 1.

We first identified potential postoperative stroke cases by searching for procedure codes possibly associated with a postoperative stroke. A manual chart review then ensued to identify which of these patients indeed suffered a postoperative stroke. We defined postoperative stroke as those diagnosed up to 30 days after surgery. This was a critical step because the procedure codes often referred to previous strokes rather than postoperative events during the index visit.

Potential controls were identified after excluding those with incomplete demographic, morphometric, or perioperative data (in addition to the exclusion criteria given above) and were matched in a 4-to-1 ratio to stroke cases using propensity scores,[15] restricting successful matches to those with common principal procedure (according to the US Agency for Healthcare Research and Quality's Clinical Classifications Software) and propensity scores within 0.01 propensity score units of one another. Partial matches, that is, those stroke patients for whom 4 suitable controls were not available, were allowed.

Statistical Analysis

Propensity scores were estimated based on patients' baseline comorbidities using multivariable logistic regression. Balance on baseline comorbidities was assessed using standardized difference scores (defined as the between-group difference in means, mean rankings, or proportions, as appropriate, divided by a combined estimate of standard deviation); any baseline variable exhibiting a standardized difference of >0.2 among the matched sample was used for adjustment in all subsequent analyses. Duration of surgery was explicitly entered into our final models as we sought to ensure strict adjustment for duration of surgery.

The primary hypotension exposure was defined as the integrated area above the MAP-versus-time curve and below the threshold of MAP = 70 mm Hg. This area under the threshold (AUT) metric, depicted in Figure 2, combines both duration and severity of hypotensive episodes into a singular measure. For example, a hypotensive episode of MAP = 60 for 10 minutes, as well as an episode of MAP = 65 for 20 minutes, would each represent an AUT of 100 mm Hg-minutes.

The distribution of the AUT measure was summarized separately for matched stroke cases and controls using standard numerical and graphical techniques. Because we expected many patients to have no hypotension below the MAP = 70 mm Hg threshold, we used a modeling technique that simultaneously models the following parameters: (1) the odds ratio for any positive AUT value comparing stroke patients with controls; and (2) the ratio of geometric mean AUT between stroke patients and controls among those with positive AUT values. The first parameter addresses the hypothesis that stroke patients may have been more likely to become hypotensive, whereas the second parameter addresses the hypothesis that, among hypotensive patients, those with perioperative stroke had more severe exposures to low MAP values. Zero-inflated negative binomial regression—adjusting for any imbalanced baseline characteristics—was used to estimate these parameters.[16]

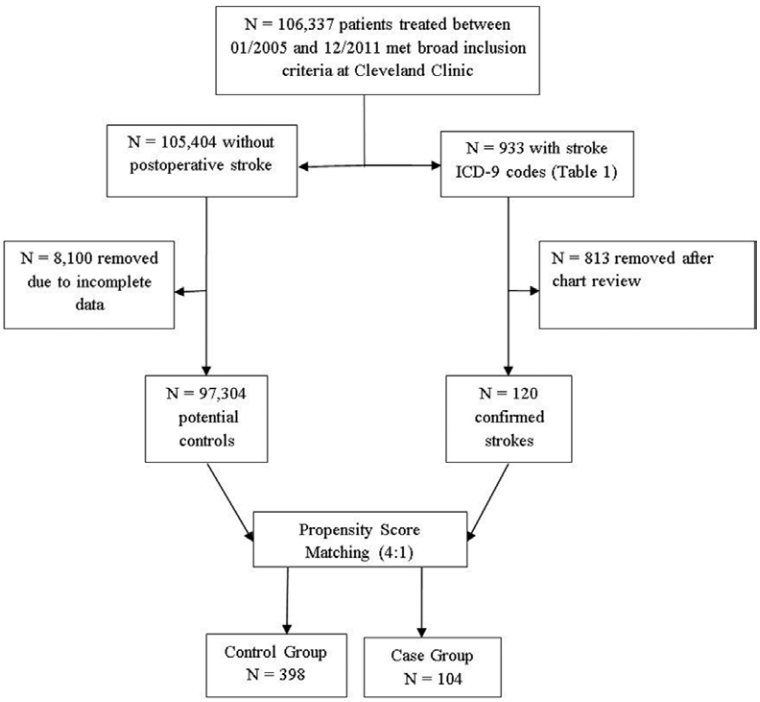

Figure 1. Patient flow diagram. *ICD-9*, *International Classification of Diseases, Ninth Revision*.

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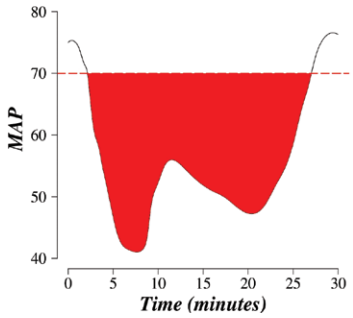

Figure 2. Example of area under threshold for a single patient defined as integrated area above mean arterial pressure (MAP) versus time curve and below the horizontal MAP = 70 mm Hg threshold.

To interrogate the effect of our choice of MAP threshold, as well as the timing of postoperative stroke on our results, sensitivity analyses were conducted using MAP thresholds of 65 and 60 mm Hg, as well as by restricting our analysis to strokes that occurred within 3 postoperative days and within 9 postoperative days. R statistical software version 3.0.0 (The R foundation for Statistical Computing, Vienna, Austria) was used for all analysis. The type I error rate for all hypothesis tests was fixed at 5%.

RESULTS

Among 106 337 patients meeting our inclusion criteria, we initially identified 933 with *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes potentially related to strokes, of which we confirmed perioperative strokes in 120 based on our manual chart review. Among 105 404 potential control patients, we excluded 8100 because of incomplete data, leaving 97 304 available for matching. Patient flow is shown in Figure 1, and the timing of postoperative stroke is represented in Figure 3.

The 4-to-1 propensity matching procedure yielded a final matched sample of 502 patients: 104 stroke cases and 398 controls. Balance was generally excellent among the matched sample, as shown in Tables 1 and 2. Thus, no variables (other than duration of surgery) were included as covariates in our regression modeling.

Distributions of the AUT measure among matched stroke cases and among matched controls were similar (Figure 3). Hypotension (ie, any MAP < 70 mm Hg) was observed in 77 of 104 (74%) stroke cases and 310 of 398 (78%) controls. Median (first quartile, third quartile) AUT values for hypotensive cases and controls were 19 (4, 55) mm Hg-minutes and 19 (6, 48) mm Hg-minutes, respectively.

Based on our zero-inflated negative binomial model, we found no associations between stroke and intraoperative hypotension as measured by AUT. The odds ratio (95% confidence interval) for any positive area (ie, any MAP < 70 mm Hg) comparing stroke cases with controls was estimated at 0.49 (0.18–1.38), which was not statistically significant (P = .18, Wald test for regression model coefficients). Among patients experiencing any intraoperative hypotension (MAP < 70 mm Hg), severity of the hypotension did not differ significantly in patients who did and did not have perioperative strokes (ratio of geometric means [95% confidence interval] of 1.07 [0.76–1.53]; P = .69).

Sensitivity analyses were performed using threshold MAP values of 65 and 60 mm Hg to define the upper bound of our AUT hypotension measure. These also failed to uncover any statistically significant relationship between intraoperative hypotension and postoperative stroke (Table 3; Supplemental Digital Content 1, Supplemental Figure 1, http://links.lww.com/AA/B485; and Supplemental Digital Content 2, Supplement Figure 2, http://links.lww.com/AA/B486). Similarly, when restricting the analysis to strokes that occurred within 3 postoperative days (n = 61) or strokes that occurred within 9 postoperative days (n = 97) and their matched controls, no remarkable trend or statistically significant relationship was found (Supplemental Digital Content 3, Supplemental Table 1, http://links.lww.com/AA/B487).

DISCUSSION

We did not identify any statistically significant or clinically important relationship between intraoperative hypotension and perioperative stroke. This differs from a previous study by Bijker et al,[13] which found that time spent >30% below baseline was associated with an increased risk of postoperative stroke. We note, however, that those investigators also found no relationship between intraoperative hypotension and postoperative stroke when using several different definitions of hypotension including raw systolic blood pressures below thresholds of 100, 90, 80, and 70 mm Hg; MAPs <70, 60, 50, and 40 mm Hg; and decreases in both systolic and mean blood pressure by 10%, 20%, and 40% from baseline.

We elected a priori not to use measures of hypotension defined relative to patient baseline blood pressure. The definition of "baseline" varies among the literature and, depending on the definition used, may affect the degree of intraoperative hypotension recorded.[17] The most consistently available baseline blood pressure values—those immediately before induction and at preoperative clinic visits—may be affected by factors such as perioperative medications, anxiety or white coat hypertension, and acute disease-related suffering; as such, they may poorly reflect patients' true baseline blood pressure levels. Rather than incorporating these variable and potentially unreliable baseline levels into our measure of hypotension, we accept the limitation that substantial interindividual differences in baseline blood pressure may decrease our ability to detect a relationship between hypotension and postoperative stroke.

Our study differs from Bijker et al[17] in not only matching patients and controls by age and type of surgery but also in the same principal procedure. By using propensity scores, which incorporate patient comorbidities, we were able to tightly match patients who did and did not experience perioperative strokes. We also excluded procedures involving the carotid arteries or proximal aorta because they have substantial potential for atheroembolic events. Finally, our study included approximately 3 times as many stroke cases.

At rest, the brain receives approximately 15% of cardiac output and is able to regulate cerebral blood flow across a range of cerebral perfusion pressures (referred to as cerebral autoregulation).[18] Traditionally, the range of blood pressures across which cerebral autoregulation is thought to maintain

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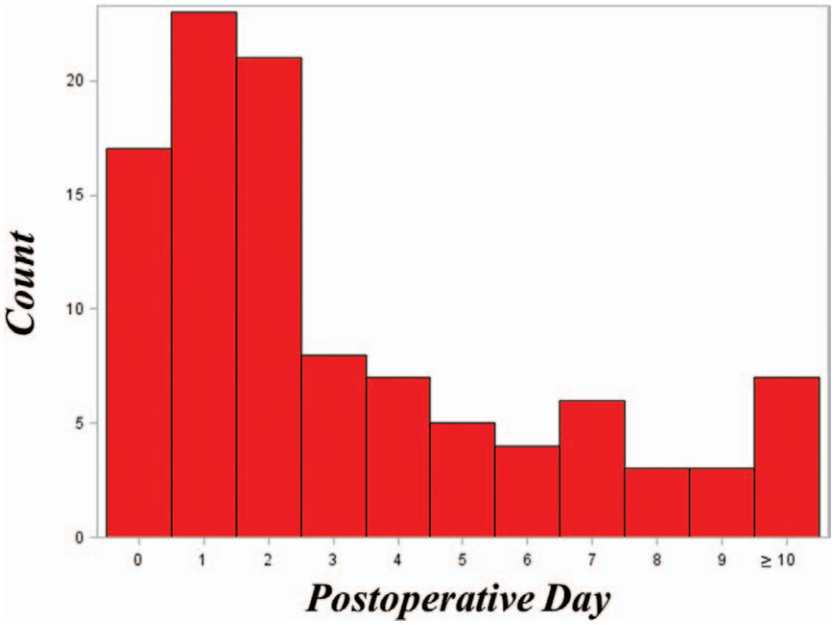

Figure 3. Histogram of timing of postoperative stroke. Seven patients with strokes after 10 days postoperatively (2 at day 11, 3 at day 12, 1 each at days 13 and 23, respectively) were included in the 10th day histogram box.

Table 1. Summary of Baseline and Intraoperative Patient Characteristics Before Matching for the Case and Control Groups

Factor	Case (n = 120)	Control (n = 97 304)	STD
Age (y)	71 ± 11	56 ± 16	1.11
BMI (kg/m^2)	28 ± 6	29 ± 8	−0.15
ASA status, n (%)			1.08
0	0 (0)	17 (0)	
1	0 (0)	5777 (6)	
2	11 (9)	41 782 (43)	
3	75 (63)	44 570 (46)	
4	34 (28)	5158 (5)	
Race, n (%)			0.09
Non-Caucasian	20 (17)	13 664 (14)	
Caucasian	97 (81)	80 378 (83)	
Unknown	3 (3)	3262 (3)	
Smoking status, n (%)			0.15
No	38 (32)	28 562 (29)	
Yes	9 (8)	11 475 (12)	
Unknown	73 (61)	57 267 (59)	
Female, n (%)	50 (42)	53 162 (55)	−0.26
Congestive heart failure, n (%)	24 (20)	3510 (4)	0.53
Valvular disease, n (%)	11 (9)	2868 (3)	0.26
Peripheral vascular disease, n (%)	40 (33)	4729 (5)	0.78
HTN, n (%)	94 (78)	43 145 (44)	0.74
Paralysis, n (%)	32 (27)	1378 (1)	0.78
Chronic pulmonary disease, n (%)	26 (22)	11 849 (12)	0.26
Diabetes w/o chronic complications, n (%)	29 (24)	15 030 (15)	0.22
Renal failure, n (%)	21 (18)	5500 (6)	0.38
Liver disease, n (%)	6 (5)	3078 (3)	0.09
Metastatic cancer, n (%)	13 (11)	5745 (6)	0.18
Coagulopathy, n (%)	37 (31)	3217 (3)	0.79
Weight loss, n (%)	42 (35)	3420 (4)	0.87
Fluid and electrolyte disorders, n (%)	65 (54)	9572 (10)	1.08
Chronic blood loss anemia, n (%)	4 (3)	1028 (1)	0.16
Alcohol abuse, n (%)	4 (3)	951 (1)	0.16
Drug abuse, n (%)	1 (1)	508 (1)	0.04
Dialysis, n (%)	7 (6)	1829 (2)	0.21
CAD, n (%)	55 (46)	11 546 (12)	0.81
Stroke or TIA, n (%)	3 (3)	512 (1)	0.16
Surgical time (min)	300 ± 188	203 ± 127	0.61

Given as "mean ± standard deviation" or "n (%)" as appropriate.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; HTN, hypertension; STD, standardized difference, before propensity score matching; TIA, transient ischemic attack.

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Table 2. Summary of Baseline and Intraoperative Patient Characteristics After Matching for the Case and Control Groups

Factor	Case (n = 104)	Control (n = 398)	STD
Age (y)	70 ± 11	72 ± 11	−0.17
BMI (kg/m^2)	28 ± 6	28 ± 7	−0.02
ASA status, n (%)			−0.03
1	0 (0)	1 (0)	
2	11 (11)	30 (8)	
3	65 (63)	263 (66)	
4	28 (27)	104 (26)	
Race, n (%)			0.10
Non-Caucasian	17 (16)	58 (15)	
Caucasian	85 (82)	327 (82)	
Unknown	2 (2)	13 (3)	
Smoking status, n (%)			0.09
No	31 (30)	126 (32)	
Yes	8 (8)	22 (6)	
Unknown	65 (63)	250 (63)	
Female, n (%)	45 (43)	180 (45)	−0.04
Congestive heart failure, n (%)	19 (18)	64 (16)	0.06
Valvular disease, n (%)	9 (9)	34 (9)	0.00
Peripheral vascular disease, n (%)	31 (30)	109 (27)	0.05
HTN, n (%)	79 (76)	319 (80)	−0.10
Paralysis, n (%)	17 (16)	45 (11)	0.15
Chronic pulmonary disease, n (%)	21 (20)	80 (20)	0.00
Diabetes w/o chronic complications, n (%)	24 (23)	103 (26)	−0.07
Renal failure, n (%)	17 (16)	68 (17)	−0.02
Liver disease, n (%)	6 (6)	21 (5)	0.02
Metastatic cancer, n (%)	10 (10)	44 (11)	−0.05
Coagulopathy, n (%)	30 (29)	101 (25)	0.08
Weight loss, n (%)	32 (31)	111 (28)	0.06
Fluid and electrolyte disorders, n (%)	53 (51)	196 (49)	0.03
Chronic blood loss anemia, n (%)	3 (3)	8 (2)	0.06
Alcohol abuse, n (%)	4 (4)	13 (3)	0.03
Drug abuse, n (%)	1 (1)	2 (1)	0.05
Dialysis, n (%)	7 (7)	19 (5)	0.08
CAD, n (%)	46 (44)	173 (43)	0.02
Stroke or TIA, n (%)	3 (3)	3 (1)	0.16
Surgical time (min)	287 ± 182	270 ± 166	0.10

Given as "mean ± standard deviation" or "n (%)" as appropriate.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; HTN, hypertension; STD, standardized difference, before propensity score matching; TIA, transient ischemic attack.

Table 3. Analyses of the Relationship Between Intraoperative Hypotension and Postoperative Stroke

Analysis Threshold	Any Hypotension Stroke Versus Control OR (95% CI)	Ratio of Geometric Mean AUT Among Hypotensive Patients Stroke Versus Control Ratio (95% CI)
Primary analysis		
<70 mm Hg	0.49 (0.18–1.38)	1.07 (0.76–1.53)
Sensitivity analyses		
<65 mm Hg	0.68 (0.27–1.71)	1.16 (0.76–1.77)
<60 mm Hg	0.72 (0.24–2.17)	1.26 (0.73–2.19)
<POD 3	0.52 (0.17–1.63)	1.63 (0.55–1.32)
<POD 9	0.51 (0.17–1.55)	1.12 (0.78–1.61)

Abbreviations: AUT, area under threshold; CI, confidence interval; POD, postoperative day; OR, odds ratio.

stable blood flow spans approximately 60 to 150 mm Hg. However, recent evidence suggests that the autoregulation range may be smaller and that cerebral blood flow may be more sensitive to hypotension than hypertension.[19]

Studies of cerebral autoregulation in humans are complicated by the need for pharmacological agents to achieve large perturbations in blood pressure homeostasis—which may affect cerebrovascular autoregulatory mechanisms—and by difficulties in accurate quantification of cerebral blood flow.[19,20] Furthermore, autoregulation during hypotension may be compromised by chronic hypertension, increased intracranial pressure, atherosclerosis, and other disease states.[21–24] A recent study of cerebral blood flow during cardiopulmonary bypass, for example, reported that the lower limit of autoregulation varied widely between patients and had no relationship with preoperative MAP.[25] These factors suggest that determination of a critical lower limit of blood pressure is complicated and highly variable between patients. In our study, we used a measure of hypotension that combined both the severity and the duration of

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hypotension experienced. In this way, our measure maintains a degree of sensitivity to differences in severity of hypotension between patients even if the threshold under investigation is higher than the "true" critical lower limit of blood pressure.

It remains possible that intraoperative hypotension contributes to perioperative strokes. Indeed, severe and prolonged intraoperative hypotension as a complication of surgery inevitably results in hypoxic damage to end organs, including the brain. A recent study reported that even short durations of hypotension (defined as MAP < 55 mm Hg) during noncardiac surgery were associated with acute kidney injury (AKI) and myocardial injury.[26] The relative scarcity of perioperative strokes (compared with postoperative AKI or myocardial infarction) and small number of patients in our sample experiencing severe degrees of intraoperative hypotension preclude the use of this threshold in our analysis. Our sensitivity analyses failed to find any relationship between hypotension and stroke at more severe degrees of hypotension (<65 and <60 mm Hg). Our results suggest that within the typical range of intraoperative blood pressures experienced at our institution, factors other than hypotension contribute more.

We also defined postoperative stroke as occurring up to 30 days after surgery. Although severe hypotensive events or surgical complications may result in strokes that manifest immediately after surgery, the majority of strokes occur between 1 day and 1 week postoperatively, and we sought to include these in our investigation. Any proposed pathological mechanism connecting intraoperative hypotension and postoperative stroke becomes more tenuous with an increasing number of postoperative days; we thus also conducted analyses restricted to strokes only occurring within 3 and 9 postoperative days. There was no substantial change in the results (Supplemental Digital Content 3, Supplemental Table 1, http://links.lww.com/AA/B487). Postoperative hypotension may be a greater contributor to later-occurring strokes than intraoperative hypotension. Postoperative blood pressure measurement is comparatively infrequent and, during the routine assessment of vital signs, patients are often stimulated, which might mask ongoing hypotensive events. The incidence of postoperative hypotension remains poorly characterized and is the subject of current investigation.

We are also limited by our definition of hypotension as <70 mm Hg and our power to detect an association at progressively greater degrees of intraoperative hypotension. A threshold of 70 mm Hg likely represents normal cerebral perfusion for a supine patient; yet, as demonstrated in Figure 4, a substantial proportion of our patients did not experience any hypotension even under this threshold. Because our measure of hypotension includes both depth and length of exposure, this renders it somewhat resilient to the choice of threshold (ie, patients with more severe hypotension will have greater exposure in the model under any chosen threshold regardless of how high); however, the relative scarcity of stroke and further reduction in the number of exposed patients under the threshold decrease our power.

We also conducted sensitivity analyses at lower thresholds for hypotension, but for these analyses the number of exposed

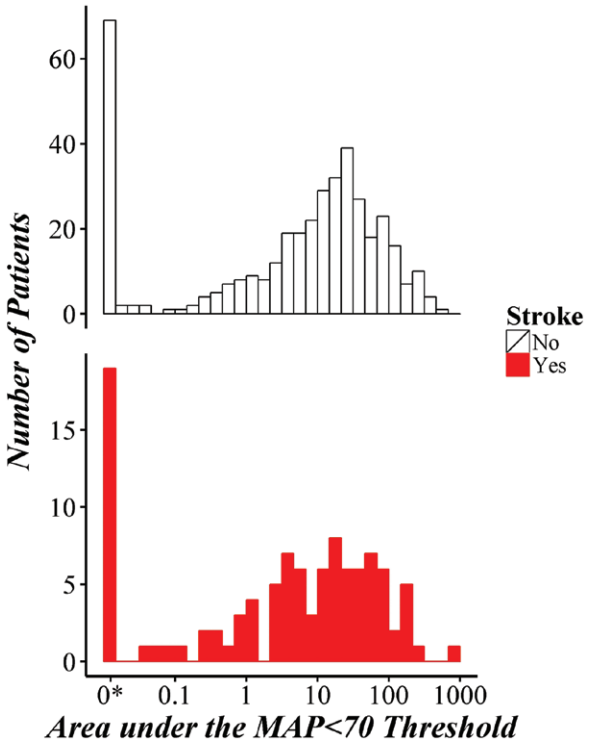

Figure 4. Histograms of stroke and control patients by degree of hypotension experienced as measured by area under 70 mm Hg. *The x-axis is presented on the logarithmic scale; area under the mean arterial pressure (MAP) = 70 mm Hg threshold values of zero, not defined under the logarithm, are concatenated to the logarithmic axis.

patients—and, therefore, our power—is reduced even further (Supplemental Digital Content 1, Supplemental Figure 1, http://links.lww.com/AA/B485; and Supplemental Digital Content 2, Supplement Figure 2, http://links.lww.com/AA/B486). It may be that we are underpowered to detect an association for this rare event using any of our thresholds. Nonetheless, our sample of over 100 postoperative strokes is the largest ever studied in this population.

Our study incorporated an observational, case-control design; it is thus possible that our results might be influenced by confounding variables unavailable in our registry. However, a randomized trial of intraoperative hypotension and postoperative stroke would be ethically challenging.

In summary, we did not find evidence of a relationship between intraoperative hypotension <70 mm Hg and postoperative stroke in adults having nonneurological, noncardiac, and noncarotid surgeries. It thus seems likely that factors other than blood pressure contribute more to the risk of postoperative stroke.

DISCLOSURES

Name: Jason K. Hsieh, BS.
Contribution: This author helped design the study, collect the data, participate in data analysis, and prepare the manuscript.
Name: Jarrod E. Dalton, PhD.
Contribution: This author helped to design the study, participated in data collection, and performed the data analysis.
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Contribution: This author helped design the study.
Name: Daniel I. Sessler, MD.
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Contribution: This author helped design the study and prepare the manuscript.
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REFERENCES

1. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology*. 2011;114:1289–1296.
2. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology*. 2011;115:879–890.
3. Hart R, Hindman B. Mechanisms of perioperative cerebral infarction. *Stroke.* 1982;13:766–773.
4. Parikh S, Cohen JR. Perioperative stroke after general surgical procedures. *N Y State J Med*. 1993;93:162–165.
5. El-Saed A, Kuller LH, Newman AB, et al. Geographic variations in stroke incidence and mortality among older populations in four US communities. *Stroke*. 2006;37:1975–1979.
6. Wong GY, Warner DO, Schroeder DR, et al. Risk of surgery and anesthesia for ischemic stroke. *Anesthesiology.* 2000;92:425–432.
7. Selim M. Perioperative stroke. *N Engl J Med*. 2007;356:706–713.
8. Bucerius J, Gummert JF, Borger MA, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg*. 2003;75:472–478.
9. McKhann GM, Grega MA, Borowicz LM Jr, Baumgartner WA, Selnes OA. Stroke and encephalopathy after cardiac surgery: an update. *Stroke*. 2006;37:562–571.
10. Kam PC, Calcroft RM. Peri-operative stroke in general surgical patients. *Anaesthesia*. 1997;52:879–883.
11. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology*. 2009;110:231–238.
12. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371:1839–1847.
13. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology*. 2012;116:658–664.
14. Limburg M, Wijdicks EF, Li H. Ischemic stroke after surgical procedures: clinical features, neuroimaging, and risk factors. *Neurology*. 1998;50:895–901.
15. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
16. Lambert D. Zero-inflated Poisson regression, with an application to defects in manufacturing. *Technometrics*. 1992;34:1–14.
17. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology*. 2007;107:213–220.
18. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39:183–238.
19. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol*. 2014;592:841–859.
20. Hamner JW, Tan CO. Relative contributions of sympathetic, cholinergic, and myogenic mechanisms to cerebral autoregulation. *Stroke*. 2014;45:1771–1777.
21. Strandgaard S, Paulson OB. Cerebral blood flow and its pathophysiology in hypertension. *Am J Hypertens*. 1989;2:486–492.
22. Guo ZN, Liu J, Xing Y, et al. Dynamic cerebral autoregulation is heterogeneous in different subtypes of acute ischemic stroke. *PLoS One.* 2014;9:e93213.
23. Brady KM, Lee JK, Kibler KK, et al. The lower limit of cerebral blood flow autoregulation is increased with elevated intracranial pressure. *Anesth Analg*. 2009;108:1278–1283.
24. Pesek M, Kibler K, Easley RB, et al. The upper limit of cerebral blood flow autoregulation is decreased with elevations in intracranial pressure. *Neurosurgery.* 2014;75:163–170.
25. Joshi B, Ono M, Brown C, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg*. 2012;114:503–510.
26. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119:507–515.

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