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Intraoperative Hypotension and Acute Kidney Injury, Stroke, and Mortality during and outside Cardiopulmonary Bypass: A Retrospective Observational Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Single-center data demonstrate that intraoperative hypotension during cardiac surgery is independently associated with stroke and acute kidney injury
- The reproducibility of this observation and whether the timing of hypotension during cardiac surgery (within *vs.* outside the cardiopulmonary bypass period) modifies the association remain unclear

What This Article Tells Us That Is New

- Among 4,984 patients undergoing cardiac surgery at a single tertiary care center between 2008 and 2016, 256 (5.1%) experienced the primary outcome of stroke (66, 1.3%), acute kidney injury (125, 2.5%), or mortality (109, 2.2%)
- Each 10 min of hypotension (mean arterial pressure of less than 65 mmHg) during, before, or after cardiopulmonary bypass was associated with an increased odds ratio of 1.06 (95% CI, 1.03 to 1.10; $P = 0.001$)
- Intraoperative hypotension, even if it occurs outside of cardiopulmonary bypass, is independently associated with stroke, acute kidney injury, or death after cardiac surgery

ABSTRACT

Background: In cardiac surgery, the association between hypotension during specific intraoperative phases or vasopressor-inotropes with adverse outcomes remains unclear. This study's hypothesis was that intraoperative hypotension duration throughout the surgery or when separated into hypotension during and outside cardiopulmonary bypass may be associated with postoperative major adverse events.

Methods: This retrospective observational cohort study included data for adults who had cardiac surgery between 2008 and 2016 in a tertiary hospital. Intraoperative hypotension was defined as mean arterial pressure of less than 65 mmHg. The total duration of hypotension was divided into three categories based on the fraction of overall hypotension duration that occurred during cardiopulmonary bypass (more than 80%, 80 to 60%, and less than 60%). The primary outcome was a composite of stroke, acute kidney injury, or mortality during the index hospitalization. The association with the composite outcome was evaluated for duration of hypotension during the entire surgery, outside cardiopulmonary bypass, and during cardiopulmonary bypass and the fraction of hypotension during cardiopulmonary bypass adjusting for vasopressor-inotrope dose, milrinone dose, patient, and surgical factors.

Results: The composite outcome occurred in 256 (5.1%) of 4,984 included patient records; 66 (1.3%) patients suffered stroke, 125 (2.5%) had acute kidney injury, and 109 (2.2%) died. The primary outcome was associated with total duration of hypotension (adjusted odds ratio, 1.05; 95% CI, 1.02 to 1.08; $P = 0.032$), hypotension outside cardiopulmonary bypass (adjusted odds ratio, 1.06; 95% CI, 1.03 to 1.10; $P = 0.001$) per 10-min exposure to mean arterial pressure of less than 65 mmHg, and fraction of hypotension duration during cardiopulmonary bypass of less than 60% (reference greater than 80%; adjusted odds ratio, 1.67; 95% CI, 1.10 to 2.60; $P = 0.019$) but not with each 10-min period hypotension during cardiopulmonary bypass (adjusted odds ratio, 1.04; 95% CI, 0.99 to 1.09; $P = 0.118$), fraction of hypotension during cardiopulmonary bypass of 60 to 80% (adjusted odds ratio, 1.45; 95% CI, 0.97 to 2.23; $P = 0.082$), or total vasopressor-inotrope dose (adjusted odds ratio, 1.00; 95% CI, 1.00 to 1.00; $P = 0.247$).

Conclusions: This study confirms previous single-center findings that intraoperative hypotension throughout cardiac surgery is associated with an increased risk of acute kidney injury, mortality, or stroke.

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Postoperative major adverse events frequently occur after cardiac surgery, especially with an increasing number of older and complex patients presenting for cardiac surgical care.[1,2] In patients having noncardiac surgery, intraoperative hypotension is associated with postoperative acute kidney

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injury (AKI),[3–5] myocardial injury,[4–6] stroke,[7] delirium,[8] and mortality.[9–11] Intraoperative hypotension may also be a modifiable risk factor for major adverse events in patients having cardiac surgery.[3,12–14]

While a mean arterial pressure (MAP) of 65 mmHg has been suggested as a population harm threshold in noncardiac surgery patients,[15] there is no clear consensus regarding an optimal blood pressure intervention threshold during cardiac surgery with cardiopulmonary bypass (CPB).[16] Existing fixed absolute blood pressure values used as lower intervention thresholds during cardiac surgery were chosen based on the principle that cerebral blood flow autoregulation remains functional during CPB.[17,18] However, current evidence suggests that lower limits of autoregulation can vary from 40 to 160 mmHg.[19] Therefore, intraoperative hypotension may be an important modifiable risk factor for major adverse events in patients having cardiac surgery. Recently, intraoperative hypotension (MAP less than 65 mmHg) even for only 11 min during CPB has been shown to increase the risk of stroke.[20]

Clinical observations and hemodynamic monitoring drive various treatments such as crystalloids, colloids, blood products, increasing pump flow, vasopressors, and inotropes during cardiac surgery. The association between organ perfusion and postoperative adverse events is complex but may be better understood when considering intraoperative pharmacologic management in addition to blood pressure. We hypothesized that intraoperative hypotension duration throughout the surgery or when separated into hypotension during and outside CPB may be associated with a composite outcome of postoperative AKI, mortality, and stroke after cardiac surgery.

In this study, we thus aimed to explore the association between (1) intraoperative hypotension (defined as MAP less than 65 mmHg) or (2) the fraction of total intraoperative hypotension occurring during CPB with a composite of three major adverse events (stroke, AKI, and mortality) accounting for intraoperative vasopressor and inotrope dose in patients having cardiac surgery with CPB.

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Materials and Methods

Study Design and Participants

In this retrospective observational cohort study, we analyzed the data that were prospectively collected in patients having cardiac surgery from institutional electronic medical records, the Society of Thoracic Surgeons (Chicago, Illinois) adult cardiac surgery database, and Anesthesia Information Systems after institutional review board approval (Beth Israel Deaconess Medical Center, Boston, Massachusetts, protocol No. 2020P000074). The institutional review board waived informed consent, and the article adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards for observational studies.[21] Data for adult patients (greater than 18 yr of age) who had cardiac surgery with CPB between January 2008 and June 2016 were included. Data for patients who underwent emergency cardiac surgery, aortic surgeries, and other procedures, such as atrial fibrillation ablation, pericardial window, maze procedure, left atrial appendage resection, septal myomectomy, and atrial septal defect closure, or invalid, incomplete, or unavailable demographic, baseline, hemodynamic, and outcome data were excluded (fig. 1).

Anesthesia Management

The perioperative details of anesthesia management have been described previously.[22] In brief, preoperative medications were continued until the time of the surgery unless contraindicated by the patient's condition. All patients received a preoperative carotid scan. Anyone with 80% or more carotid stenosis on either side or symptoms suggestive of carotid stenosis was consulted with vascular surgery for appropriate management before surgery. All patients underwent general anesthesia with endotracheal intubation. Standard IV induction was performed using IV propofol and fentanyl. Rocuronium was used for muscle relaxation and isoflurane (0.5 to 1%) for maintenance. Valvular surgeries were performed under cardiac arrest using a standard institutional cardioplegia solution (60 mEq potassium, 8 mEq magnesium, 2.5 g dextrose, 10 mEq Tromethamine, and 500 ml normal saline). The patients were maintained under mild hypothermia, and an α-stat pH strategy was used for blood gas management during CPB.

Hemodynamic Monitoring

All patients received transoesophageal echocardiography (TEE) monitoring throughout the surgery unless contraindicated. The rate, rhythm, preload, afterload, and contractility were maintained with information obtained from arterial catheters, pulmonary artery or central venous catheters, and TEE. All cardiac anesthesiologists involved in patient care were TEE board–certified. After induction, IV phenylephrine or norepinephrine infusions were started to maintain a systolic blood pressure of 90 to 120 mmHg.

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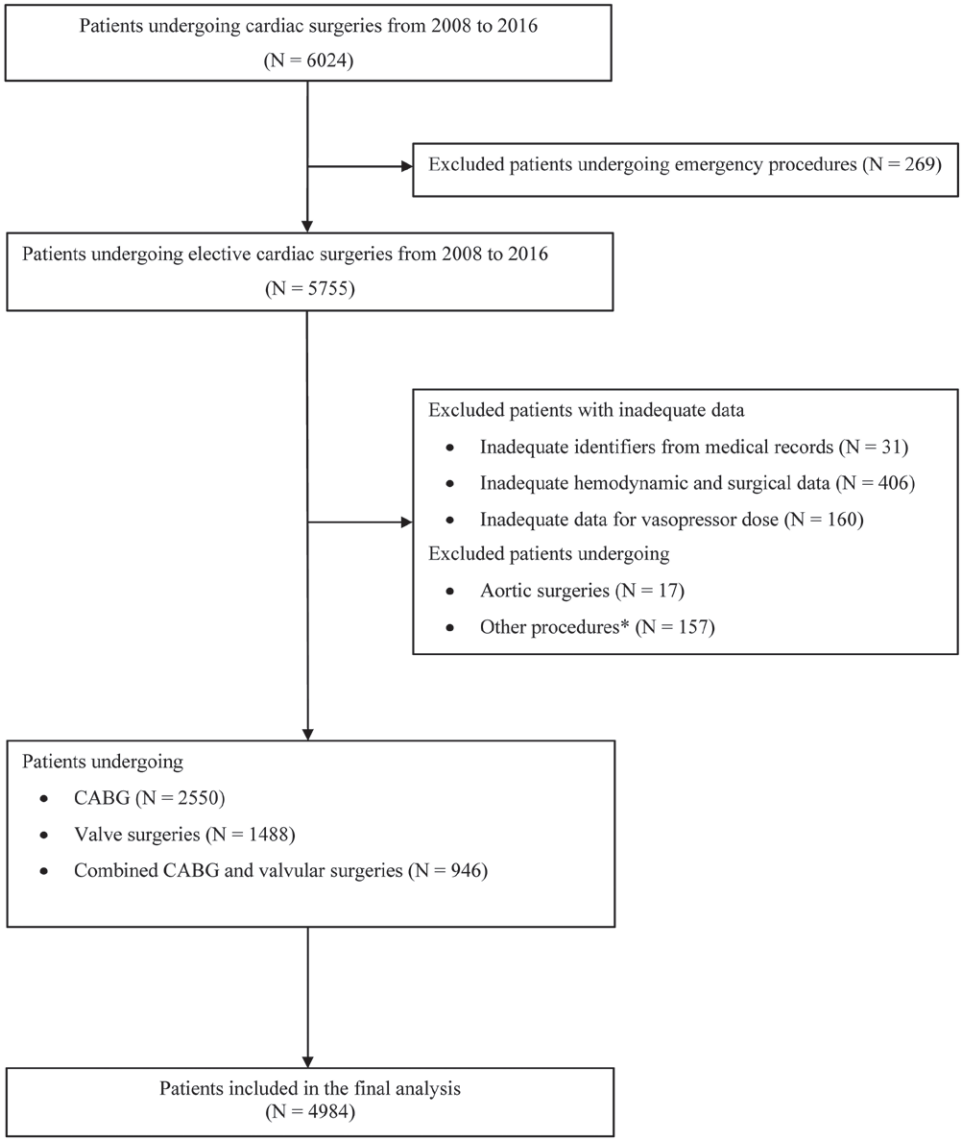

Fig. 1. Flow chart presenting patient selection and analysis. *Other procedures include atrial fibrillation ablation, pericardial window, maze procedure, left atrial appendage resection, septal myomectomy, and atrial septal defect closure. CABG, coronary artery bypass graft.

Vasopressor and Inotrope Treatment

After CPB, in patients with low to moderately dysfunctional ventricular function (preoperative left ventricular ejection fraction less than 30% or with significant mitral or aortic regurgitation), IV epinephrine was started to maintain a cardiac index greater than 2 $l \cdot min^{-1} \cdot m^{-2}$. Intravenous milrinone was added to this regimen to achieve the same goals at the clinician's discretion. Other medications, such as dopamine and dobutamine, were rarely added to this strategy. Afterload was maintained with phenylephrine, norepinephrine, or both, either by themselves or along with the inotropes. The management was guided by direct visualization of the ventricles, echocardiographic assessment of cardiac function with or without pulmonary artery catheter measurements of mixed venous oxygen saturation, and cardiac index.

Vasopressor-inotrope dose was calculated by adding norepinephrine equivalents of total norepinephrine, epinephrine, phenylephrine, and vasopressin dose used during surgery, using the following formula: total vasopressor-inotrope dose = [norepinephrine (μg/min) × min] + [epinephrine (μg/min) × min] + [(phenylephrine (μg/min) × min) ÷ 10] + [vasopressin (U/h) × 8.33 × min].[23,24] The total dose of milrinone used was obtained from the database and analyzed separately.

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Definition of Intraoperative Hypotension

Invasive blood pressure was recorded every 15 s, and artifacts were removed using the rules that were previously described.[5,25] Intraoperative hypotension was defined as MAP less than 65 mmHg per the noncardiac surgical literature.[15] It was characterized by (1) total duration as cumulative minutes and (2) area under a MAP of 65 mmHg (area under the receiver operating characteristics curve [AUC]–MAP 65 mmHg) measured based on the trapezoidal rule.[10,26] Using this method, values below the threshold were subtracted from the threshold, multiplied by 0.25 (which corresponds to 15 s), and summed together. For example, each MAP value x less than 65 mmHg will be subtracted from 65, multiplied by 0.25 min, and all such values were summed together.

$$\text{AUC} = \Sigma\left[(65 - x) \times 0.25\right] \text{ mmHg} \times \text{min}$$

Intraoperative Hypotension during CPB

The duration of intraoperative hypotension was divided into three categories based on how much of the total intraoperative hypotension occurred during CPB (fraction of intraoperative hypotension during CPB): (1) more than 80%, (2) 80 to 60% (inclusive), and (3) less than 60%.

Study Outcome

The primary outcome was a composite of three major adverse events: (1) stroke, defined as any confirmed postoperative neurologic deficit of abrupt onset caused by a disturbance in cerebral blood supply that did not resolve within 24 h; (2) AKI, defined as one or both of the following: threefold rise in serum creatinine from baseline or a creatinine level greater than 4.0 mg/dl with a minimum rise of 0.5 mg/dl and/or a new requirement for dialysis postoperatively; and (3) mortality, defined as all deaths, regardless of cause, occurring during the hospitalization in which the surgery was performed, even if after 30 days (including patients transferred to other acute care facilities) or all deaths, regardless of cause, occurring after discharge from the hospital, but before the end of postoperative day 30, based on Society of Thoracic Surgeons definition, version 2.73 (Supplemental Digital Content 1, appendix 1, http://links.lww.com/ALN/C817). Stroke or AKI occurring during the index hospitalization, even if more than 30 days, was included in the primary outcome.

Statistical Analysis

Descriptive statistics were computed as mean values with SD for continuous variables and frequencies with percentages for categorical variables. The Kruskal–Wallis test was used for normality testing. Continuous (normal and nonnormal) and categorical measures were appropriately tested with t tests, Wilcoxon rank sum tests, and chi-square tests, respectively. Multivariable logistic regression models were used to assess the association between intraoperative hypotension per 10-min exposure to MAP less than 65 mmHg, AUC-MAP 65 mmHg, vasopressor-inotrope dose, total dose of milrinone, and the composite primary outcome (primary model). Confounders were predefined based on clinical plausibility, which included age in years, sex, surgery category, Society of Thoracic Surgeons risk scores in tertiles, preoperative left ventricular ejection fraction, change in hematocrit percentage, and aortic cross-clamp time. The same confounders were used for both intraoperative hypotension variables (total duration per 10-min exposure to MAP less than 65 mmHg and AUC-MAP 65 mmHg) analyses. We introduced the statistically ($P < 0.10$ in the univariable analysis) and clinically significant variables into the model. The total duration of intraoperative hypotension per 10-min exposure to MAP less than 65 mmHg and AUC-MAP 65 mmHg were considered as two separate multivariable analyses. In an attempt to determine the phase-specific associations of intraoperative hypotension during cardiac surgery, we constructed similar multivariable logistic regression models exploring the relationship between hypotension duration per 10-min exposure to MAP less than 65 mmHg during and outside CPB with the composite primary outcome. Similar models were used to explore the association between the fraction of hypotension duration during CPB (greater than 80%, 80 to 60%, and less than 60%) with the composite outcome and individual major adverse events.

The linearity assumption of the effects of intraoperative hypotension, vasopressor-inotrope dose, and total dose of milrinone on the log odds of the outcome variable was assessed using restricted cubic splines with three knots and generalized additive models. In the cases in which significant nonlinear terms were detected, the corresponding variables were categorized using tertiles/quartiles. The effect modification of vasopressor-inotrope dose and total dose of milrinone on the association between intraoperative hypotension and the composite outcome was evaluated by including an interaction term of vasopressor-inotrope dose and intraoperative hypotension in the logistic regression models. In the case of nonsignificant interaction, the final model only with main effects was reported. The Hosmer–Lemeshow goodness-of-fit test and AUC were used to assess the model fit. The precision-recall AUC was reported given the class imbalance in this data set. The variable inflation factor was used to assess the correlation between predictors. Intraoperative hypotension duration was introduced into the model as a restricted cubic spline for measuring the predicted probabilities of the composite primary outcome. Statistical analyses were performed in R version 3.5.1 and RStudio version 1.1.463 (RStudio, USA). All tests were two-sided, with 0.05 as the level of significance. Correction for multiple testing and models was not performed. No specific power calculation was performed for this retrospective

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observational cohort study. The data analysis and statistical plan were written after the data were accessed.[27]

Sensitivity Analyses

We performed two sensitivity analyses to further explore the robustness of the association between intraoperative hypotension and the composite primary outcome. The first sensitivity analysis was designed to examine the association between total duration and AUC-MAP 65 mmHg with the composite outcome wherein we used preoperative comorbid conditions as the variables in the multivariable logistic regression models instead of the Society of Thoracic Surgeons risk score. Although we used the Society of Thoracic Surgeons risk score, which itself includes all preoperative comorbidities, in addition to multiple other perioperative variables in our primary analyses, we wanted to examine the association when considering individual comorbidities. The second sensitivity analysis was designed to eliminate the potential impact of outlier cases with an extremely long duration of hypotension. Accordingly, we excluded the top 5% of patients from our final cohort and determined the association between total hypotension duration and AUC-MAP 65 mmHg with the composite outcome. Our primary model in this study evolved as a result of the peer review process, and we focused on specific models following the suggestions from reviewers and editors.

Results

Baseline Characteristics

Figure 1 displays an overview of patient selection and analysis. Data describing 6,024 patients who had cardiac surgeries from 2008 to 2016 were collected. We excluded 269 patients who had emergent surgeries. From the remaining 5,755 patients, 597 patients were excluded due to inadequate data; 174 patients who underwent procedures other than coronary artery bypass graft, valve, or combined were excluded; and the final analysis included 4,984 patients. Table 1 summarizes the baseline characteristics of patients stratified by the postoperative composite outcome. The mean ± SD age of our study population was 67 ± 11 yr. There were 3,491 (70%) male patients, 1,165 (23%) patients had diabetes, 3,933 (79%) patients had hypertension, and 3,807 (76%) patients had dyslipidemia. Previous myocardial infarction was present in 1,565 (31%), congestive heart failure was present in 1,741 (35%), and 85 (2%) patients were on dialysis before surgery.

Postoperative Major Adverse Events

Postoperative major adverse events are displayed in Supplemental Digital Content 2 (table 1, http://links.lww.com/ALN/C818). The composite primary outcome occurred in 256 (5.1%). AKI was present in 125 (2.5%) patients, 66 (1.3%) patients had a stroke, and 109 (2.2%) patients died after surgery. Baseline characteristics of patients stratified by the composite primary outcome are presented in table 1. Patients having one of the major adverse events of the composite primary outcome were significantly older and more likely to be male and have diabetes (table 1). They also had a higher incidence of congestive heart failure, previous myocardial injury, chronic lung disease, and need for inotropic support and steroid medications as compared to those without the composite primary outcome. Society of Thoracic Surgeons risk scores were statistically significantly higher in patients with the composite primary outcome compared to those without (mean ± SD, 0.05 ± 0.06 *vs.* 0.02 ± 0.03; $P < 0.001$).

In addition, patients with the composite primary outcome had a statistically significant increased mean ± SD CPB time (121 ± 61 *vs.* 93 ± 36 min; $P < 0.001$), cross-clamp time (89 ± 42 *vs.* 73 ± 29 min; $P < 0.001$], duration of MAP less than 65 mmHg (143 ± 75 *vs.* 104 ± 48 min; $P < 0.001$) and AUC-MAP 65 mmHg (1,528 ± 1,134 *vs.* 1,070 ± 656 mmHg/min; $P < 0.001$) compared to those without the composite primary outcome. Similarly, median (interquartile range) vasopressor-inotrope dose (milligrams) was statistically significantly higher in patients with the composite primary outcome compared to those without the composite primary outcome (0.98 [0.53 to 2.24] *vs.* 0.65 [0.36 to 1.07] mg; $P < 0.001$; table 1).

Association between Intraoperative Hypotension, Vasopressor-Inotrope Dose, Total Dose of Milrinone, and the Composite Primary Outcome

Every 10-min increase in intraoperative hypotension duration of MAP less than 65 mmHg, AUC-MAP 65 mmHg, vasopressor-inotrope dose, and total dose of milrinone were categorized as continuous variables. The results of multivariable logistic regression analysis evaluating the association between the total duration of intraoperative hypotension throughout the surgery and the composite primary outcome are displayed in table 2. The association of total duration of intraoperative hypotension per 10-min exposure to MAP less than 65 mmHg with the composite primary outcome was statistically significant (adjusted odds ratio, 1.05; 95% CI, 1.02 to 1.08; $P = 0.032$). No statistically significant associations were observed for vasopressor-inotrope dose or the total dose of milrinone (adjusted odds ratio, 1.00; 95% CI, 1.00 to 1.00; $P = 0.247$; and adjusted odds ratio, 1.00; 95% CI, 0 to 1.00; $P = 0.648$).

Statistically significant associations were seen with intraoperative hypotension defined as AUC-MAP 65 mmHg throughout the surgery and the composite outcome (adjusted odds ratio, 1.00; 95% CI, 1.00 to 1.00; $P < 0.001$; Supplemental Digital Content 3, table 2, http://links.lww.com/ALN/C819). However, no statistically significant associations were seen with vasopressor-inotrope dose or total dose of milrinone (adjusted odds ratio, 1.00; 95% CI,

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Table 1. Demographics and Clinical Characteristics Stratified by Composite Primary Outcome

Demographics	All Patients (N = 4,984)	Composite Primary Outcome*		*P* Value†
		Absent (N = 4,728 [94.8])	Present (N = 256 [5.1])	
Age, yr, mean ± SD	67 ± 12	67 ± 12	71 ± 12	< 0.001
Male	3,491 (70)	3,329 (70)	162 (63)	0.019
Diabetes	1,165 (23)	1,090 (23)	75 (29)	0.026
Dyslipidemia	3,807 (76)	3,606 (76)	201 (79)	0.454
Hypertension	3,933 (79)	3,713 (79)	220 (86)	0.006
Smoking	1,435 (29)	1,357 (29)	78 (31)	0.591
Congestive heart failure	1,741 (35)	1,590 (34)	151 (59)	< 0.001
Previous myocardial infarction	1,565 (31)	1,458 (31)	107 (42)	< 0.001
Chronic lung disease	596 (12)	547 (12)	49 (19)	< 0.001
Dialysis	85 (2)	79 (2)	6 (2)	0.574
Ejection fraction	54.08 (14)	54.17 (14)	52.45 (15)	0.050
Preoperative medications				
β-Blockers	3,741 (75)	3,554 (75)	187 (73)	0.490
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	2,195 (44)	2,085 (44)	110 (43)	0.772
Inotropes	44 (0.9)	32 (0.7)	12 (4.7)	< 0.001
Steroids	168 (3.4)	149 (3.2)	19 (7.4)	< 0.001
Aspirin	4,147 (83)	3,942 (83)	205 (80)	0.197
Statins	3,886 (78)	3,689 (78)	197 (77)	0.745
Society of Thoracic Surgeons risk score, mean ± SD	0.02 ± 0.03	0.02 ± 0.03	0.05 ± 0.06	< 0.001
Surgery category				< 0.001
Coronary artery bypass grafting	2,550 (51)	2,466 (52)	84 (33)	
Coronary artery bypass grafting and valve	946 (19)	854 (18)	92 (36)	
Valve	1,488 (30)	1,408 (30)	80 (31)	
Duration of phase, min, mean ± SD				
Cardiopulmonary bypass	95 ± 38	93 ± 36	121 ± 61	< 0.001
Aortic cross-clamp time	74 ± 30	73 ± 29	89 ± 42	< 0.001
Hematocrit change, mean ± SD	2.77 ± 8	2.82 ± 8	1.84 ± 8	0.066
Colloids, ml, mean ± SD	474 ± 181	472 ± 188	500 ± 0	0.839
Crystalloids, ml, mean ± SD	2,957 ± 3,313	2,951 ± 3,391	3,081 ± 1,045	0.545
Duration MAP less than 65 mmHg, min, mean ± SD	106 ± 51	104 ± 48	143 ± 75.34	< 0.001
Area under the curve–MAP less than 65 mmHg, mmHg · min, mean ± SD	1,094 ± 696	1,070 ± 656	1,528 ± 1,135	< 0.001
Vasopressor-inotrope dose (median), mg [interquartile range]	0.66 [0.37–1.10]	0.65 [0.36–1.07]	0.98 [0.53–2.24]	< 0.001
Milrinone dose (median), mg [interquartile range]	0.00 [0.00–0.00]	0.00 [0.00–0.00]	0.00 [0.00–0.00]	< 0.001

The data are presented as numbers (percentages) unless otherwise indicated.

*Composites of acute kidney injury, stroke, and mortality. †*P* values from chi-square test, Student's *t* test, or Wilcoxon rank sum test, as appropriate.

MAP, mean arterial pressure.

1.00 to 1.00; $P = 0.475$; and adjusted odds ratio, 1.00; 95% CI, 0 to 1.00; $P = 0.756$; Supplemental Digital Content 3, table 2, http://links.lww.com/ALN/C819).

The relationship between the total duration of intraoperative hypotension (quartiles), vasopressor-inotrope dose (quartiles), and the composite primary outcome rate is shown in figure 2. A higher total duration of hypotension and vasopressor-inotrope dose was associated with a higher composite primary outcome incidence (fig. 2). While assessing the model fit, the models demonstrated an average AUC of 0.761 and precision-recall AUC of 0.164.

Association between Hypotension during CPB Phase, outside CPB Phase, and the Composite Primary Outcome

Tables 3 and 4 illustrate the results of multivariable logistic regression models examining the association between duration of hypotension per 10-min exposure to MAP less than 65 mmHg during and outside the CPB phase with the composite primary outcome. Statistically significant associations were seen with hypotension per 10-min exposure to MAP less than 65 mmHg (adjusted odds ratio, 1.06; 95% CI, 1.03 to 1.10; $P = 0.001$) outside the CPB phase and the composite outcome. However, hypotension per 10-min exposure to MAP less than 65 mmHg during CPB phase (adjusted odds ratio, 1.04; 95% CI, 0.99 to 1.09; $P = 0.118$) was not associated with the primary outcome.

Association between the Fraction of Hypotension during CPB and the Composite Primary Outcome

The association between varying fractions of hypotension during CPB and the composite primary outcome is presented in table 5. When compared with more than 80% hypotension duration occurring during CPB, exposure

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Table 2. Association between Total Duration of Intraoperative Hypotension per 10-min Exposure to MAP Less than 65 mmHg, Vasopressor-Inotrope Dose, Milrinone Dose, and Composite Primary Outcome

Variables	Odds Ratio	95% CI*	*P* Value
Age	1.00	0.99–1.02	0.699
Female	1.04	0.78–1.39	0.851
Category			
CABG and valve	1.10	0.77–1.61	0.521
Valve	1.05	0.74–1.50	0.730
Change in hematocrit	0.99	0.97–1.00	0.101
Ejection fraction	1.00	0.99–1.01	0.815
Duration of surgery	1.04	1.01–1.07	< 0.001
Aortic cross-clamp time	1.00	0.99–1.00	0.295
Society of Thoracic Surgeons risk score†			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.62	1.00–2.69	0.046
Tertile 3	5.05	3.06–8.50	< 0.001
MAP less than 65 mmHg per 10 min	1.05	1.02–1.08	0.032
Vasopressor-inotrope dose	1.00	1.00–1.00	0.247
Milrinone dose	1.00	0.00–1.00	0.648

*Composite of acute kidney injury, stroke, and mortality adjusted for age, sex, type of surgery, Society of Thoracic Surgeons risk score, left ventricular ejection fraction, Change in hematocrit percentage, duration of surgery, and cross-clamp time. †Society of Thoracic Surgeons risk score categorized into tertiles: less than 0.01, 0.01 to 0.02, and greater than 0.02 to 0.52.

CABG, coronary artery bypass grafting; MAP, mean arterial pressure.

to 80 to 60% of hypotension during CPB was not statistically significantly associated with the primary composite outcome (adjusted odds ratio, 1.45; 95% CI, 0.97 to 2.23; $P = 0.082$), while less than 60% of hypotension occurring during CPB was statistically significantly associated with the primary composite outcome (odds ratio, 1.67; 95% CI, 1.10 to 2.60; $P = 0.019$). The associations between varying fractions of hypotension occurring during CPB with individual components of the composite outcome are presented in Supplemental Digital Content 4 (table 3, http://links.lww.com/ALN/C820).

Sensitivity Analyses

The association between the total duration of hypotension per 10-min exposure to MAP less than 65 mmHg and AUC-MAP 65 mmHg with the composite primary outcome remained statistically significant in sensitivity analyses. In the model that included preoperative comorbidities instead of the Society of Thoracic Surgeons risk score (Supplemental Digital Content 5, table 4, http://links.lww.com/ALN/C821), both duration and AUC-MAP 65 mmHg were statistically significantly associated with the composite primary outcome (adjusted odds ratio, 1.00; 95% CI, 1.00 to 1.01; $P = 0.002$; and adjusted odds ratio, 1.00; 95% CI, 1.00 to 1.00; $P = 0.017$). Similarly, in the other sensitivity analysis that explored similar associations excluding the top 5% of patients who had an extremely long duration of hypotension (Supplemental Digital Content 6, table 5, http://links.lww.com/ALN/C822), the relationship between duration and AUC-MAP 65 mmHg was similar to our primary analysis (adjusted odds ratio, 1.01; 95% CI, 1.00 to 1.01; $P < 0.001$; and adjusted odds ratio, 1.00; 95% CI, 1.00 to 1.00; $P = 0.002$).

Missing Data

Supplemental Digital Content 7 (table 6, http://links.lww.com/ALN/C823) illustrates the results of demographic information comparing patients included in the final cohort and patients who were excluded due to missing data.

Predicted Probabilities of the Composite Primary Outcome

Supplemental Digital Content 8 (fig. 1, http://links.lww.com/ALN/C824) presents the predicted probabilities of the composite primary outcome plotted against the total duration of intraoperative hypotension. The top 5% of the cohort have extremely long durations of hypotension (approximately 200 min; Supplemental Digital Content 8, fig. 1A, http://links.lww.com/ALN/C824). Supplemental Digital Content 8 (fig. 1B, http://links.lww.com/ALN/C824) presents a similar relationship excluding this top 5% of patients from the final cohort. Supplemental Digital Content 9 (fig. 2, http://links.lww.com/ALN/C825) illustrates the predicted probabilities of the composite primary outcome with vasopressor-inotrope dose (Supplemental Digital Content 9, fig. 2A) and the total dose of milrinone (Supplemental Digital Content 9, fig. 2B).

Supplemental Digital Content 10 (fig. 3, http://links.lww.com/ALN/C826) demonstrates the distribution of the Society of Thoracic Surgeons risk score among the final cohort of patients. We could observe the nonlinearity of the Society of Thoracic Surgeons risk score among the cohort.

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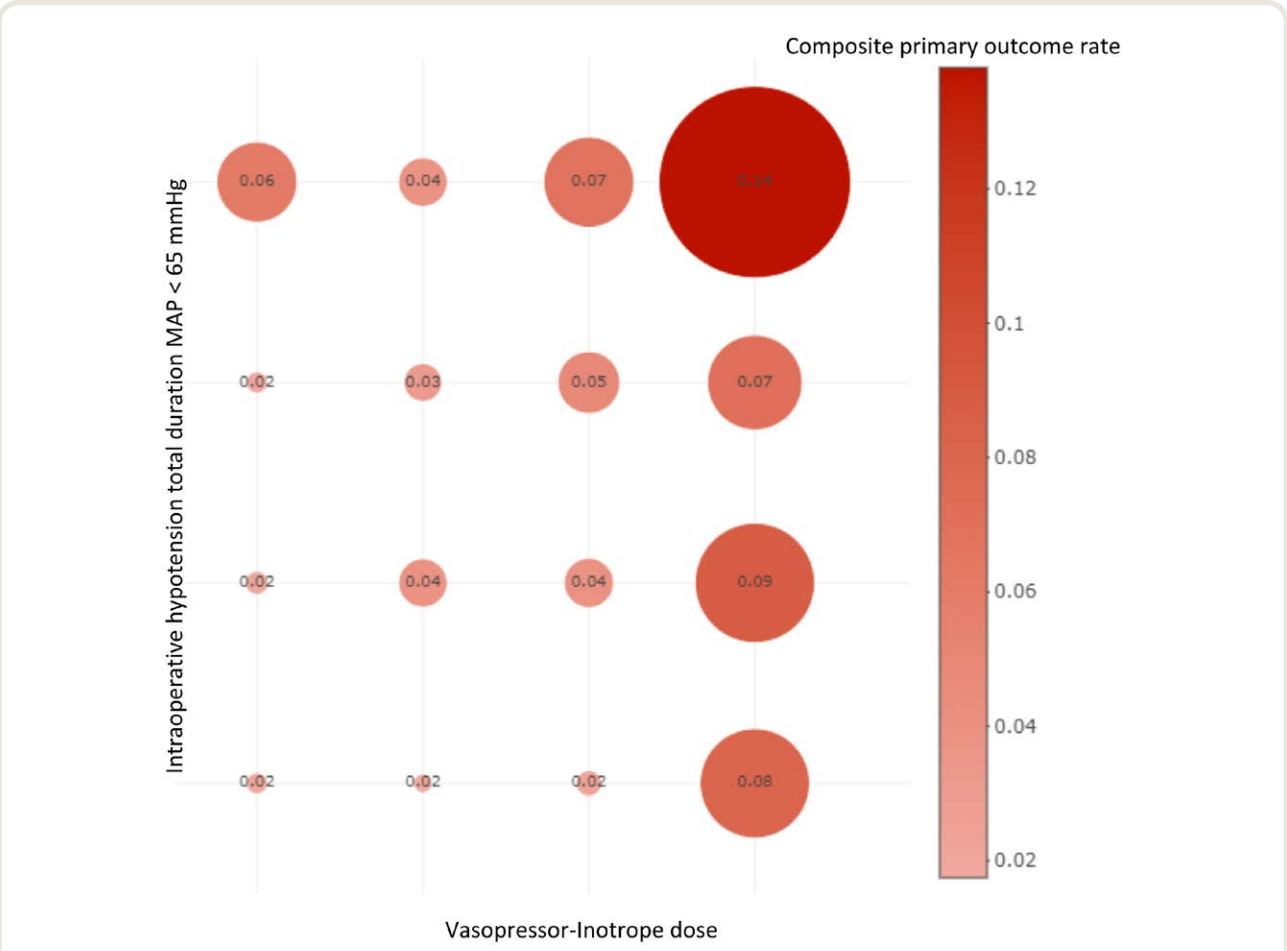

Fig. 2. Association between total duration of intraoperative hypotension mean arterial pressure (MAP) less than 65 mmHg, vasopressor-inotrope dose, and composite primary outcome. The *x axis* corresponds to vasopressor-inotrope dose in quartiles, whereas the *y axis* corresponds to the total duration of intraoperative hypotension MAP less than 65 mmHg in quartiles. *Bubble size* and *color* represent composite primary outcome rate.

Supplemental Digital Content 11 (fig. 4, http://links.lww.com/ALN/C827) illustrates the correlation between intraoperative hypotension total duration with vasopressor-inotrope dose, total dose of milrinone, Society of Thoracic Surgeons risk score, age, sex, surgery category, hematocrit change, ejection fraction, duration of surgery, and cross-clamp time. We provide open access to all our data extraction, filtering, data wrangling, modeling, figures, and table code and queries at https://github.com/theonesp/vasopressor_dose_mae.

Discussion

In patients undergoing cardiac surgery with CPB, the total duration of intraoperative hypotension per 10-min exposure of MAP less than 65 mmHg throughout the surgery was statistically significantly associated with the composite primary outcome of stroke, AKI, or death. Similar associations were seen with the duration of intraoperative hypotension outside the CPB phase and composite primary outcome.

We observed a significant association between intraoperative hypotension during cardiac surgery and adverse outcomes. These results broadly support the work of previous research showing that hypotension during cardiac surgery was significantly associated with stroke,[20] renal injury,[28] and mortality.[29] Similar to this research, in studies exploring the CPB phase–specific hypotension in patients undergoing cardiac surgery, the risk of postoperative stroke[20] and renal replacement therapy[28] increased for every 10-min exposure to MAP less than 65 mmHg.

In addition to duration, we characterized the severity of intraoperative hypotension as AUC-MAP 65 mmHg. Both total intraoperative hypotension duration and AUC-MAP 65 mmHg showed similar results. Our results were consistent with previous studies,[5,25] in which both the duration and AUC for blood pressure thresholds were associated with adverse outcomes.

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Table 3. Association between Intraoperative Hypotension per 10-min Exposure to MAP Less than 65 mmHg during CPB Phase, Vasopressor-Inotrope Dose, Milrinone Dose, and Composite Primary Outcome

Variables	Odds Ratio	95% CI*	*P* Value
Age	1.00	0.99–1.02	0.679
Female	1.02	0.77–1.37	0.846
Category			
CABG and valve	1.12	0.77–1.63	0.545
Valve	1.09	0.77–1.55	0.636
Change in hematocrit	0.98	0.97–1.00	0.080
Ejection fraction	1.00	0.99–1.01	0.780
Duration of surgery	1.05	1.03–1.08	< 0.001
Aortic cross-clamp time	1.00	0.99–1.00	0.171
Society of Thoracic Surgeons risk score†			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.67	1.03–2.76	0.042
Tertile 3	5.40	3.29–9.06	< 0.001
MAP less than 65 mmHg during CPB phase per 10 min	1.04	0.99–1.09	0.118
Vasopressor-inotrope dose	1.00	1.00–1.00	0.243
Milrinone dose	1.00	0.00–1.00	0.632

*Composite of acute kidney injury, stroke, and mortality adjusted for age, sex, type of surgery, Society of Thoracic Surgeons risk score, left ventricular ejection fraction, Change in hematocrit percentage, duration of surgery, and cross-clamp time. †Society of Thoracic Surgeons risk score categorized into tertiles: less than 0.01, 0.01 to 0.02, and greater than 0.02 to 0.52.
CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

Table 4. Association between Intraoperative Hypotension per 10-min Exposure to MAP Less than 65 mmHg, Outside CPB Phase, Vasopressor-Inotrope Dose, Milrinone Dose, and Composite Primary Outcome

Variables	Odds Ratio	95% CI*	*P* Value
Age	1.00	0.99–1.01	0.843
Female	1.01	0.76–1.34	0.940
Category			
CABG and valve	1.12	0.77–1.62	0.567
Valve	1.09	0.77–1.54	0.637
Change in hematocrit	0.99	0.97–1.00	0.117
Ejection fraction	1.00	0.99–1.01	0.798
Duration of surgery	1.05	1.02–1.07	< 0.001
Aortic cross-clamp time	1.00	0.99–1.00	0.703
Society of Thoracic Surgeons risk score†			
Tertile 1	Reference	Reference	
Tertile 2	1.62	0.99–1.01	0.057
Tertile 3	5.00	3.03–8.42	< 0.001
MAP less than 65 mmHg outside CPB phase per 10 min	1.06	1.03–1.10	0.001
Vasopressor-inotrope dose	1.00	1.00–1.00	0.235
Milrinone dose	1.00	0.00–1.00	0.645

*Composite of acute kidney injury, stroke and mortality adjusted for age, sex, type of surgery, Society of Thoracic Surgeons risk score, left ventricular ejection fraction, Change in hematocrit percentage, duration of surgery, and cross-clamp time. †Society of Thoracic Surgeons risk score categorized into tertiles: less than 0.01, 0.01 to 0.02, and greater than 0.02 to 0.52.
CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

When exploring an intraoperative phase–specific relationship with adverse events, hypotension duration outside the CPB phase was significantly associated with the primary outcome. Our results mirror the findings of a similar study in which MAP less than 65 mmHg for 10 min or more during the post-CPB phase significantly increased the risk of adverse events.[28] Compared with the fraction of overall hypotension duration occurring during CPB of more than 80%, a fraction of hypotension duration occurring during CPB of less than 60% was statistically significantly associated with a higher risk of the composite outcome. This observation may be explained by the physiologic stress during the post-CPB phase. Various mechanisms such as catecholamine surges, mechanical trauma to red blood cells triggering inflammatory states, and decreased vasomotor reactivity after CPB in the presence of hypotension could worsen end-organ damage, resulting in adverse outcomes. It is possible, therefore, that hypotension outside the CPB

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Table 5. Association between Fraction of Intraoperative Hypotension Duration during CPB and Composite Primary Outcome

Variables	Odds Ratio	95% CI*	*P* Value
Age	1.00	0.99–1.02	0.782
Female	1.01	0.75–1.33	0.972
Category			
CABG and valve	1.16	0.80–1.70	0.431
Valve	1.19	0.84–1.68	0.324
Change in hematocrit	0.98	0.97–1.00	0.081
Ejection fraction	1.00	1.00–1.01	0.971
Duration of surgery	1.01	1.00–1.01	< 0.001
Aortic cross-clamp time	1.00	0.99–1.01	0.972
Society of Thoracic Surgeons risk score†			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.56	0.97–2.55	0.069
Tertile 3	4.41	2.70–7.35	< 0.001
Fraction of intraoperative hypotension duration during CPB (MAP less than 65 mmHg)			
80 to 60%	1.45	0.97–2.23	0.082
Less than 60%	1.67	1.10–2.60	0.019
Vasopressor-inotrope dose	1.00	1.00–1.00	0.247
Milrinone dose	1.00	0–1.00	0.639

*Composite of acute kidney injury, stroke, and mortality adjusted for age, sex, type of surgery, Society of Thoracic Surgeons risk score, left ventricular ejection fraction, Change in hematocrit percentage, duration of surgery, and aortic cross-clamp time. †Society of Thoracic Surgeons risk score categorized into tertiles: less than 0.01, 0.01 to 0.02, and greater than 0.02.
CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

phase is an important risk factor that needs to be taken into consideration, and more research is needed regarding the effects of hypotension during and outside CPB.[30,31]

Advanced hemodynamic monitoring and protocolized treatment strategies in the cardiac surgical setting can identify and treat hemodynamic changes earlier than in noncardiac surgery with noninvasive monitoring. In this study, we did not observe a statistically significant association between vasopressor-inotrope dose or total dose of milrinone and the composite outcome. Even though vasopressor-inotropes were used to treat hypotension using advanced hemodynamic monitoring, the duration of intraoperative hypotension was still associated with the composite outcome.

Transesophageal echocardiography, invasive arterial blood pressure monitoring, and central venous pressures were routinely used in our care setting to optimize fluids and maintain blood pressures throughout cardiac surgery. In this context, vasopressor use to optimize blood pressures was not associated with a higher or lower incidence of major adverse events in our study. Other studies have shown a similar lack of reduction in postoperative adverse outcomes with the use of vasopressors to achieve higher MAP thresholds.[22,32–34] It remains to be explored whether vasopressor treatment aiming to achieve a fixed intraoperative blood pressure target (*e.g.*, MAP of 65 mmHg) could improve postoperative outcomes.

Weis *et al.*[35] observed that cardiac surgical patients needing more vasopressors had a greater degree of a systemic inflammatory response that has been associated with poor outcomes.[36] Moreover, significant associations between increased vasopressor support and renal replacement therapy, length of stay, and periods of ventilation after cardiac surgery were reported.[35]

The relationship between organ perfusion and adverse outcomes remains complex and has recently gained increased scientific attention. Further work is needed to gain a better understanding regarding markers such as oxygen delivery as a measure for tissue perfusion.

This is a retrospective study, and finding a causative link between intraoperative hypotension or vasopressor-inotrope dose and postoperative outcomes is thus not possible. Moreover, the vasopressor-inotrope dose was calculated by adding norepinephrine equivalents of vasopressors and inotropes used. As each drug might have a different molecular target, there is a possibility that we might have missed the effect of an individual medication. The sample size may be relatively small to evaluate the true interaction between intraoperative hypotension, vasopressor-inotrope dose, and outcome. Our analyses did not include data reflecting postoperative hypotension and other factors related to tissue perfusion, such as mixed venous oxygen saturation or blood gas parameters that might have an association with the incidence of adverse outcomes. In addition, our analysis is limited by a possible lack of power for many of the nonsignificant observations and lack of adjustment for multiple testing.

To conclude, in patients having cardiac surgery with CPB, the total duration of intraoperative hypotension per 10-min exposure of MAP less than 65 mmHg was statistically significantly associated with the composite primary outcome of stroke, AKI, or mortality. Hypotension per 10-min exposure of MAP less than 65 mmHg outside the CPB phase was statistically significantly associated with the composite outcome. These results confirm findings from previous studies exploring the intraoperative phase–specific

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association between hypotension and adverse outcomes. Vasopressor-inotrope dose or total dose of milrinone was not statistically significantly associated with the composite primary outcome.

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Competing Interests

Dr. Saugel has received honoraria for consulting, honoraria for giving lectures, and refunds of travel expenses from Edwards Lifesciences Inc. (Irvine, California). He has received honoraria for consulting, institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from Pulsion Medical Systems SE (Feldkirchen, Germany). Dr. Saugel has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria). He has received institutional restricted research grants from Retia Medical LLC. (Valhalla, New York). He has received honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany). Dr. Saugel has received honoraria for consulting, institutional restricted research grants, and refunds of travel expenses from Tensys Medical Inc. (San Diego, California). The other authors declare no competing interests.

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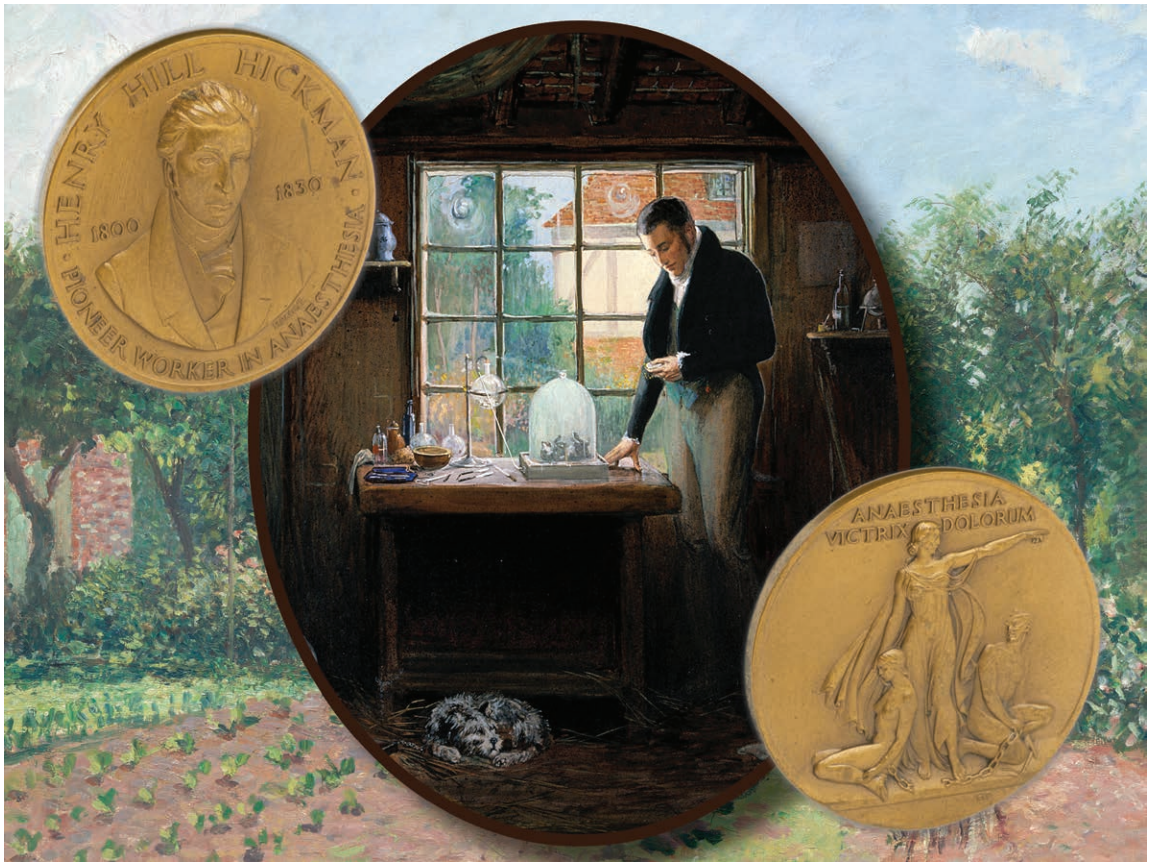
Only Half Dead: Henry H. Hickman and "Suspended Animation"



Appalled by the plight of surgical patients before the advent of ether anesthesia, English physician Henry Hill Hickman (1800 to 1830, *center*) championed "suspended animation" as an anesthetic technique. He induced hypercapnic narcosis and transient respiratory arrest by enclosing puppies in glass chambers (*center*). At times, he infused supplemental carbon dioxide to expedite the process. Thereby sedated, the canines would tolerate the removal of parts of their ears without associated pain, hemorrhage, or inflammation. By contrast, the same procedure performed on awake dogs would cause discomfort, bleeding, and edema. Eager to disseminate his findings, Hickman sought the patronage of scientist T. A. Knight of England and King Charles X of France, to no avail. During his short lifetime, no scientific community would endorse his use of controlled asphyxia, which sometimes required rescue insufflation. However, a century after his death, Hickman would be immortalized. Seeking to raise the profile of a burgeoning specialty, the Anaesthetic Section of the Royal Society of Medicine would endow an international honor in his name. Since 1935, the Hickman Medal has been given every 3 years to a physician or scientist with outstanding contributions to anesthesia. The one pictured above, with an image of Hickman on its obverse (*upper left*), and a woman depicting "*Anaesthesia, Victrix Dolorum*" on its reverse (*lower right*), was awarded to Ralph Waters, M.D. (1883 to 1979), pioneer of American academic anesthesiology. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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