ANESTHESIOLOGY

Association between In-hospital Mortality and Low Cardiac Output Syndrome with Morning *versus* Afternoon Cardiac Surgery

A Retrospective Cohort Study

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ABSTRACT

Background: Recent work suggests that having aortic valve surgery in the morning increases risk for cardiac-related complications. This study therefore explored whether mortality and cardiac complications, specifically low cardiac output syndrome, differ for morning and afternoon cardiac surgeries.

Methods: The study included adults who had aortic and/or mitral valve repair/replacement and/or coronary artery bypass grafting from 2011 to 2018. The components of the in-hospital composite outcome were in-hospital mortality and low cardiac output syndrome, defined by requirement for at least two inotropic agents at 24 to 48 h postoperatively or need for mechanical circulatory support. Patients who had aortic cross-clamping between 8 and 11 AM (morning surgery) *versus* between 2 and 5 PM (afternoon surgery) were compared on the incidence of the composite outcome.

Results: Among 9,734 qualifying operations, 0.4% (29 of 6,859) died after morning, and 0.7% (20 of 2,875) died after afternoon surgery. The composite of in-hospital mortality and low cardiac output syndrome occurred in 2.8% (195 of 6,859) of morning patients and 3.4% (97 of 2,875) of afternoon patients: morning *versus* afternoon confounder-adjusted odds ratio, 0.96 (95% CI, 0.75 to 1.24; $P = 0.770$). There was no evidence of interaction between morning *versus* afternoon and surgery type ($P = 0.965$), and operation time was statistically nonsignificant for surgery subgroups.

Conclusions: Patients having aortic valve surgery, mitral valve surgery, and/or coronary artery bypass grafting with aortic cross-clamping in the morning and afternoon did not have significantly different outcomes. No evidence was found to suggest that morning or afternoon surgical timing alters postoperative risk.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Whether complications differ with morning and afternoon cardiac surgery remains unclear

What This Article Tells Us That Is New

- A retrospective cohort study evaluated 9,734 patients who had aortic valve, mitral valve, and/or coronary artery bypass graft surgery over 7 yr at a single center
- The confounder-adjusted incidence of the composite outcome of in-hospital low cardiac output syndrome or mortality was similar for morning and afternoon surgery
- The results do not support selective morning or afternoon scheduling for cardiac surgery

There is conflicting evidence as to whether late-in-the-day scheduling of cardiac surgery alters postoperative complications. Worse outcomes may be related to reduced availability of personnel and hospital resources or provider fatigue,[1] whereas other possible explanations include nonrandom timing for severe illness and emergent cases.[2] In contrast, others found no difference in morbidity and mortality when cardiac procedures were performed in the morning *versus* afternoon[3–5] or overnight.[6–8] Higher mortality and morbidity after noncardiac surgery have also been reported when they occur late in the day,[9–13] although some report no difference.[14–16] None of these investigations reported higher risk with morning surgery.

In contrast, a recent retrospective investigation (N = 596) by Montaigne *et al.*[17] demonstrated higher myocardial infarction, heart failure, and cardiovascular death when aortic valve replacement surgery occurred in the morning, with worse outcomes attributed to reduced myocardial ischemic tolerance. The same investigators randomized 88 patients to morning *versus* afternoon aortic valve replacement surgery and reported that postoperative troponin concentrations were 20% greater after morning surgery.

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of the work presented in this article was presented virtually at the American Society of Anesthesiologists Annual Meeting on October 3, 2020 (Session EA19-4, Perioperative Medicine IV). This article has a visual abstract available in the online version.

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Various factors, such as fewer available providers and provider fatigue, may contribute to worse outcomes in the afternoon. In contrast, many biologic processes, including tolerance to myocardial ischemia, may be governed by circadian rhythms and vary by time of day with worse outcomes in the morning. In nonsurgical patients, for example, myocardial infarctions are more severe in the morning. Patients who experience myocardial ischemia from midnight to 6 AM develop larger myocardial infarcts, more heart failure, and worse left ventricular dysfunction than those with ischemia in the afternoon.[18–20] The large prospective First Acute Myocardial Infarction study reported that ST-segment elevation myocardial infarctions are more likely between 6 AM and noon.[21] Whether cardiac-related complications are increased after aortic valve surgery with respect to morning risk remains unclear. Given previous conflicting studies, we tested the hypothesis that the incidence of a composite of mortality and low cardiac output syndrome is higher for morning than afternoon surgery when adjusted for previously identified risk factors.

Materials and Methods

This retrospective, observational, single-center cohort study was approved by the Cleveland Clinic Institutional Review Board with waived informed consent. We obtained data from the Cleveland Clinic Perioperative Health Documentation System, the Automated Record Keeper System (electronic intraoperative anesthesia record), and our institutional Society of Thoracic Surgeons database. Patient data were linked across databases through medical record numbers and dates of surgery. Variable definitions and data sources are reported in Supplemental Digital Content, table 1 (http://links.lww.com/ALN/C559). This report follows the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) and STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Patient Population

We initially limited our investigation to patients having aortic valve replacement; however, postoperative mortality and complications after aortic valve surgery are rare at our institution. We therefore broadened our inclusion criteria and considered all adults who had elective aortic valve replacement/repair, mitral valve replacement/repair, and/or coronary artery bypass grafting with cardiopulmonary bypass between 2010 and 2018 at the Cleveland Clinic main campus with aortic cross-clamp start times between 8 AM and 5 PM.

We excluded patients who had end-stage renal disease requiring renal replacement therapy, elevated baseline troponin T, myocardial infarction within 7 days preoperatively, aortic cross-clamp start time before 8 AM or after 5 PM, emergent surgery, heart transplantation, lung transplantation, preoperative cardiogenic shock, and patients who were scheduled for insertion of right or left ventricular assist device.

Post hoc, we realized that surgical approach was not recorded for patients who had surgery in 2010 and was only sometimes recorded for patients who had surgery from January to June 2011, most likely because of a change in data collection protocol. Because surgical approach was an important confounder, associated with both exposure and outcome, we restricted our analysis to patients who had surgery from January 1, 2011, to December 31, 2018. Patients who were missing surgical approach from the first half of year 2011 were excluded under a complete case analysis, assuming missing at random for all missing variables.

Exposure Variable: Morning *versus* Afternoon Case

Patients were divided into morning and afternoon groups based on their aortic cross-clamp start times. Patients with aortic cross-clamp start times between 8 and 11 AM were defined as having morning surgery, and those with aortic cross-clamp start times between 2 and 5 PM were defined as having afternoon surgery. Patients with aortic cross-clamp application between 11 AM and 2 PM were not included in the primary analysis to provide clear separation between the groups. All patients were followed until hospital discharge.

Clinical Processes of Care

Standard American Society of Anesthesiologists (Schaumburg, Illinois) monitors, brachial arterial catheters, central venous or pulmonary artery catheters, and transesophageal echocardiography were used for all patients. Anesthesia was induced and maintained with midazolam, fentanyl, propofol, etomidate, ketamine, methadone, depolarizing and/or nondepolarizing muscle relaxants, and volatile anesthetics. Standard procedures were used for initiation and separation from cardiopulmonary bypass. Intermittent retrograde and antegrade Buckberg or del Nido cardioplegia were given for cardioplegic arrest. Low cardiac index during separation from cardiopulmonary bypass was treated with epinephrine, milrinone, dobutamine, or dopamine infusion to achieve a cardiac index of more than $2.0\ \mathrm{l \cdot min^{-1} \cdot m^{-2}}$. The indications for use of two or more inotropic agents include continued hemodynamic instability caused by myocardial failure/insufficiency assessed by pulmonary artery catheters with a cardiac index of less than $2.0\ \mathrm{l \cdot min^{-1} \cdot m^{-2}}$ or left and/or right ventricular dysfunction assessed by echocardiography after optimizing preload and afterload and correction of all electrolyte and blood gas abnormalities. Hypotension with adequate intravascular volume status was treated with norepinephrine or vasopressin infusion for a target mean arterial pressure of more than 70 mmHg.

Study Endpoints

The primary endpoint was a composite outcome of in-hospital mortality and/or low cardiac output syndrome. Low

cardiac output syndrome was defined as one or both of the following criteria:

(1) The need for two or more inotropic agents (epinephrine, milrinone, dobutamine, or high-dose dopamine [more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$]) at 24 to 48 h postoperatively with one or more of the following: (i) a documented low cardiac output (less than 2.0 $l \cdot min^{-1} \cdot m^{-2}$) postcardiopulmonary bypass and/or immediately after surgery in the intensive care unit; (ii) left and/or right ventricular dysfunction on intraoperative postcardiopulmonary bypass transesophageal echocardiography; and (iii) chart documentation of postoperative cardiac insufficiency/cardiogenic shock. The need for vasopressor support (norepinephrine, vasopressin, phenylephrine) without the use of two or more inotropic agents (epinephrine, milrinone, dobutamine, or high-dose dopamine [more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$]) does not fulfill the criteria for low cardiac output syndrome.
(2) Use of mechanical circulatory support with extracorporeal membrane oxygenation, left ventricular assist device, or intraaortic balloon pump within the first five postoperative days to treat patients with refractory cardiac failure despite the use of multiple inotropic support. Patients who required extracorporeal membrane oxygenation for pulmonary insufficiency were excluded.

This clinically relevant outcome of low cardiac output syndrome was selected because it was associated with a 12-fold increase in risk for postoperative mortality after cardiac surgery in a large cross-sectional observational analysis that included more than 59,000 patients.[22] Importantly, those with low cardiac output syndrome comprised greater than 60% of postoperative deaths.

Statistical Analysis

The Institutional Review Board–approved protocol included a detailed statistical analysis plan describing all variables required for the analysis, including the primary and secondary outcomes, exposure variables, and confounder variables, which were defined *a priori* before accession of the data. We initially planned to limit our analysis to patients having aortic valve replacement surgery, as in a previous analysis that demonstrated worse myocardial ischemic tolerance with morning surgery.[18] However, the event rate is low in our aortic valve replacement surgery population, with an overall mortality of only ≈0.24% and low cardiac output syndrome of ≈1.2%. We therefore modified our statistical plan (before the data were accessed) by including more complex and combination procedures to increase the power and generalizability of our analysis.

Our *a priori* developed statistical plan included a primary composite outcome of mortality and/or low cardiac output syndrome and a secondary outcome of postoperative troponin concentrations. Patients with low cardiac output syndrome were identified by the need for postoperative hemodynamic support with two or more inotropic agents and/or need for mechanical circulatory support. Database and/or chart review were performed to confirm that patients who required two or more inotropic agents also received two or more inotropic agents at the end of surgery (to confirm that myocardial insufficiency began intraoperatively rather than following a postoperative complication) and also exhibited one or more characteristics consistent with low cardiac output syndrome, including a documented low cardiac index, left and/or right ventricular dysfunction, and/or postoperative cardiac insufficiency/cardiogenic shock as described above.

For troponin T concentrations, blood for troponin assessment in our institution is routinely sampled just once at approximately 2 AM of the first postoperative morning. *Post hoc*, we realized that there were thus substantial systematic differences in the time elapsed between surgery and the troponin assay in the morning and afternoon groups, making the results uninterpretable. We therefore modified our *a priori* developed statistical plan and did not compare the prespecified secondary outcome of troponin concentrations.

Potential confounding factors including demographic characteristics, baseline comorbidities, preoperative medications, and surgery type were adjusted with stabilized propensity score weighting, in which the propensity score was calculated as the probability of cross-clamp occurring in the morning. The weight was then calculated for morning patients as the proportion of morning patients divided by the propensity score and for afternoon patients as the proportion of afternoon patients divided by (1 − propensity score). Balance in confounding factors between morning and afternoon was assessed through absolute standardized difference, and any confounding factors with an absolute standardized difference of more than 0.10 were treated as imbalanced and adjusted for in the main analysis model.

The association between aortic cross-clamp start time (morning *vs.* afternoon) and the incidence of the collapsed outcome were assessed through a logistic regression model. The interaction between aortic cross-clamp start time and surgery type was assessed at significance level of 0.15, and subgroup analyses were performed for each type of surgery whether or not interactions were significant. All tests were performed two-sided.

In an *a priori* planned sensitivity analysis, we treated aortic cross-clamp start time as a continuous exposure including data from all patients who had application of aortic cross-clamp between 8 AM and 5 PM and assessed the association between cross-clamp start time and the incidence of the composite outcome through a logistic regression model, with confounding factors adjusted for directly in the model. Linearity of the association was visually checked by incorporating a restricted cubic spline term with smoothing parameter of 0.10 into the model. Upon finding a nonlinear association, we instead estimated the difference between each hour.

Post Hoc Sensitivity Analyses in Response to Reviewer Feedback

After the statistically nonsignificant association between cross-clamp hour and the outcome, we further assessed the association between surgery start hour and the composite outcome. Logistic regression with direct adjustment for confounding variables was used to assess the association, with surgery start hour analyzed as a categorical variable.

To adjust for a potential unmeasured surgical factor, we performed an analysis that included a variable for the attending surgeon in the propensity score. The surgeon was excluded if she/he usually operated at a specific time of day and performed either four or fewer surgeries in the morning, or four or fewer surgeries in the afternoon during the entire study time frame.

We also assessed the difference between morning *versus* afternoon patients on other major postoperative complications as defined by the Society of Thoracic Surgeons (Chicago, Illinois) including stroke, renal failure, prolonged ventilation, deep sternal wound infections, and cardiac reoperation.[23] All the outcomes were assessed through logistic regression, with confounders adjusted through stabilized inverse probability of treatment weighting, as described above. Because the analysis was exploratory, Bonferroni correction was not applied.

Only our statistical team had access to raw data. SAS 9.4 statistical software (USA) and *R* statistical software version 3.5.1 for 64-bit Windows operating system (R Foundation for Statistical Computing, Austria) were used for all data processing and analyses.

Sample Size Considerations

A low incidence of mortality (0.24%) and low cardiac output syndrome (1.18%) after aortic valve replacement at our center would require a sample size of 386,000 patients for 90% power to detect a difference in our composite outcome, which was not feasible. When mitral valve and coronary artery bypass grafting procedures were included, 9,734 patients and an incidence of 3% in the composite outcome provided 90% power to detect an odds ratio of 1.50 or higher comparing morning patients to afternoon patients.

Results

We identified 15,349 cardiac surgeries from 15,224 patients that met inclusion and exclusion criteria from January 1, 2011, through December 31, 2018. The last index cardiac surgery for each patient was considered in the analysis. For this cohort, we assessed the missing pattern for the baseline variables, including surgical approach, and proceeded with a complete case analysis involving 13,344 patients (fig. 1).

Primary Analysis

For the main analysis, we included 9,734 patients who had aortic cross-clamping started between 8 and 11 AM or 2 and 5 PM. In 6,859 (70.5%) patients, aortic cross-clamping occurred in the morning (8 to 11 AM), and 2,875 (29.5%) had aortic cross-clamping in the afternoon (2 to 5 PM). Morning patients had less severe left ventricular dysfunction, fewer previous myocardial infarctions, and less preoperative aspirin use. The two groups were also imbalanced in year of surgery, surgical approach, and surgical procedure. All baseline confounding variables were balanced after propensity score weighting (table 1).

The raw incidence of mortality was 0.5% (49 of 9,734) overall, 0.4% (29 of 6,859) for morning surgery, and 0.7% (20 of 2,875) for afternoon surgery (morning *vs.* afternoon unadjusted odds ratio, 0.61; 95% CI, 0.34 to 1.07; $P = 0.086$) The raw incidence of low cardiac output syndrome was 2.7% (263 of 9,734) overall, 2.6% (175 of 6,859) for morning surgery, and 3.1% (88 of 2,875) for afternoon surgery (morning *vs.* afternoon unadjusted odds ratio, 0.83; 95% CI, 0.64 to 1.08; $P = 0.158$). The perioperative profiles of patients with low cardiac output are summarized in Supplemental Digital Content, table 2 (http://links.lww.com/ALN/C559). The incidence of the collapsed composite outcome of in-hospital mortality and/or low cardiac output syndrome was 3.0% (292 of 9,734) overall, 2.8% (195 of 6,859) for morning surgery, and 3.4% (97 of 2,875) for afternoon surgery (morning *vs.* afternoon unadjusted odds ratio, 0.84; 95% CI, 0.65 to 1.07; $P = 0.162$). The incidence of mortality and low cardiac output syndrome by surgery type is listed in table 2. The median (quartile 1, quartile 3) length of hospital stay was 7 (6, 10) days for morning patients and 8 (6, 10) days for afternoon patients.

Intraoperative use of inotropic and vasopressor medications, including epinephrine, norepinephrine, milrinone, dopamine, dobutamine, and vasopressin, was similar between groups. Intraoperative medications, blood product transfusion, and other descriptive variables are summarized in table 3.

The incidence of the composite outcome did not differ significantly when comparing morning and afternoon surgery, with an adjusted odds ratio estimated at 0.96 (95% CI, 0.75 to 1.24; $P = 0.770$). The interaction between morning *versus* afternoon and surgery type was also statistically nonsignificant ($P = 0.965$), and the time effect was nonsignificant in all of the surgery type subgroups (table 2).

Post Hoc Sensitivity Analyses

We included 13,344 patients whose surgeries had aortic cross-clamp started between 8 AM and 5 PM. The incidence of the composite outcome was similar across aortic cross-clamp start hours (overall $P = 0.989$; fig. 2), suggesting no significant variation by time. We also assessed the incidence of the composite outcome against surgery start hour. Because our usual surgery start time is 7 AM on weekdays, a large number of surgery start times were clustered between 6:45 and 7:15. We thus partitioned the surgery start time at

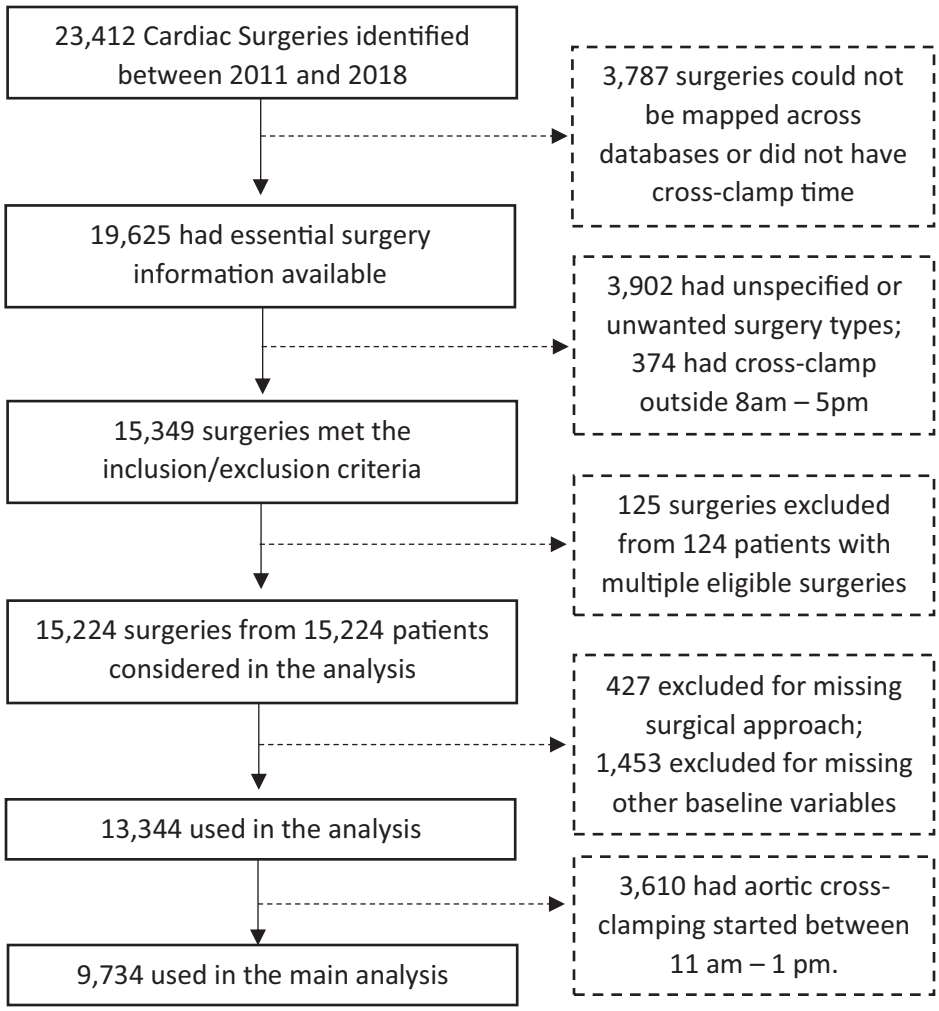

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) patient flow chart.

the half hour after every full hour (*e.g.*, 7:30 AM, 8:30 AM, *etc.*). Overall, there was not a significant association (overall $P = 0.291$; Supplemental Digital Content, table 3, http://links.lww.com/ALN/C559).

We included and balanced for individual surgeons after propensity score matching. Consistent with the primary results, no difference between morning and afternoon surgeries was found, with estimated odds ratio of 1.00 (95% CI, 0.78 to 1.29; $P = 0.987$) comparing morning to afternoon.

We also compared the two groups on major postoperative morbidity as defined by the Society of Thoracic Surgeons. Afternoon patients had more prolonged ventilation ($P = 0.036$), but no difference was found for other postoperative complications, including stroke, renal failure, deep sternal wound infection, and cardiac reoperation. These results are summarized in Supplemental Digital Content, table 4 (http://links.lww.com/ALN/C559).

Discussion

The composite outcome of mortality and low cardiac output syndrome did not differ in patients who had morning *versus* afternoon aortic valve, mitral valve, and/or coronary artery bypass grafting surgery. The results were consistent regardless of procedural type. The results were also consistent regardless of whether surgical timing was considered dichotomously or as a continuous variable. Comparing surgery start time rather than aortic cross-clamp start time also provided consistent results.

The absence of time-of-day variation in postoperative cardiac complications in our patients contrasts with the results of Montaigne *et al.*,[17] who reported more major adverse cardiac events and higher postoperative troponin T concentrations in patients having aortic valve replacement (with or without coronary artery bypass grafting) in the morning. Although we evaluated various types of cardiac

Table 1. Baseline Variables before and after Stabilized Inverse Probability of Treatment Weighting (N = 9,734)

	Before Weighting			After Weighting		
Variable	Morning (N = 6,859)	Afternoon (N = 2,875)	Absolute Standardized Difference	Morning	Afternoon	Absolute Standardized Difference
Demographics						
Age, yr	64 ± 13	65 ± 12	0.058	64 ± 13	64 ± 13	0.004
Female	2,371 (35)	1,005 (35)	0.008	2,381 (35)	1,005 (35)	0.006
Body mass index, kg/m^2	28 ± 6	29 ± 6	0.043	28 ± 6	28 ± 6	0.005
Medical history						
Hypertension	5,158 (75)	2,239 (78)	0.063	5,216 (76)	2,189 (76)	0.004
Atrial fibrillation or flutter	998 (15)	503 (17)	0.080	1,060 (15)	446 (16)	0.002
Heart failure	859 (13)	421 (15)	0.062	906 (13)	385 (13)	0.005
Coronary artery disease	2,515 (37)	1,101 (38)	0.034	2,552 (37)	1,077 (37)	0.006
Left ventricular dysfunction			0.118			0.004
Normal	2,747 (40)	1,295 (45)		2,779 (40)	1,163 (40)	
Mild	421 (6)	1,196 (42)		447 (7)	186 (6)	
Moderate	67 (1)	216 (8)		80 (1)	33 (1)	
Moderate–severe	3,404 (50)	48 (2)		3,315 (48)	1,388 (48)	
Severe	220 (3)	120 (4)		242 (4)	103 (4)	
Myocardial infarction	657 (10)	389 (14)	0.124	737 (11)	308 (11)	0.001
Pulmonary hypertension	9 (0)	6 (0.2)	0.019	11 (0.1)	5 (0.2)	0.002
Chronic obstructive pulmonary disease	224 (3)	111 (4)	0.032	237 (3)	102 (4)	0.005
Moderate or severe mitral insufficiency	3,032 (44)	1,353 (47)	0.057	3,092 (45)	1,288 (45)	0.005
Carotid artery stenosis	878 (13)	384 (13)	0.016	890 (13)	380 (13)	0.007
Peripheral vascular disease	504 (7)	259 (9)	0.061	541 (8)	230 (8)	0.005
Diabetes mellitus	1,398 (20)	624 (22)	0.032	1,427 (21)	606 (21)	0.007
Cerebral vascular accident	440 (6)	193 (7)	0.012	447 (7)	191 (7)	0.006
Preoperative medication						
Aspirin	1,464 (21)	739 (26)	0.103	1,554 (23)	656 (23)	0.004
β-Adrenergic blocking agents	2,372 (35)	1,052 (37)	0.042	2,418 (35)	1,020 (35)	0.005
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1,789 (26)	832 (29)	0.064	1,848 (27)	773 (27)	0.001
Statins	1,667 (24)	781 (27)	0.065	1,729 (25)	730 (25)	0.005
Diuretics	1,597 (23)	701 (24)	0.026	1,626 (24)	694 (24)	0.010
Preoperative laboratory values						
Hematocrit, %	41 ± 4	41 ± 4	0.059	41 ± 4	41 ± 4	0.006
Creatinine, mg/dl	1.0 ± 0.3	1.0 ± 0.3	0.006	1.0 ± 0.3	1.0 ± 0.3	0.003
Glucose, mg/dl	105 ± 33	106 ± 36	0.036	106 ± 33	106 ± 35	0.002
Surgical characteristics						
Duration of surgery, min	364 ± 95	371 ± 110	0.069	366 ± 92	367 ± 110	0.010
Cardiopulmonary bypass time, min	96 ± 42	99 ± 41	0.069	97 ± 42	98 ± 41	0.015
Aortic cross-clamp time, min	74 ± 33	76 ± 33	0.069	75 ± 34	75 ± 34	0.018
Surgical approach			0.186			0.010
Median sternotomy	4,762 (69)	2,211 (77)		4,918 (72)	2,066 (72)	
Mini sternotomy	1,191 (17)	424 (15)		1,136 (17)	466 (16)	
Robot-assisted thoracoscopy	68 (1)	22 (1)		63 (1)	26 (1)	
Thoracotomy	838 (12)	218 (8)		745 (11)	315 (11)	
Reoperative surgery	1,017 (15)	414 (14)	0.012	1,013 (15)	433 (15)	0.009
Surgical procedure			0.259			0.013
Aortic valve replacement	1,994 (29)	663 (23)		1,876 (27)	796 (28)	
Aortic valve replacement + ascending aorta replacement	145 (2)	51 (2)		138 (2)	57 (2)	
Aortic valve replacement + coronary artery bypass grafting	581 (8)	273 (9)		604 (9)	255 (9)	
Aortic valve replacement + coronary artery bypass grafting + other	125 (2)	56 (2)		127 (2)	54 (2)	
Aortic valve replacement + mitral valve surgery	424 (6)	165 (6)		416 (6)	177 (6)	
Coronary artery bypass grafting	665 (10)	456 (16)		791 (12)	331 (12)	
Coronary artery bypass grafting + mitral valve repair	199 (3)	151 (5)		246 (4)	103 (4)	
Coronary artery bypass grafting + mitral valve replacement	78 (1)	52 (2)		89 (1)	36 (1)	
Mitral valve repair	2136 (31)	820 (29)		2081 (30)	859 (30)	
Mitral valve replacement	512 (7)	188 (7)		493 (7)	205 (7)	
Year of surgery			0.142			0.009
2011	533 (8)	243 (8)		546 (8)	230 (8)	
2012	877 (13)	403 (14)		904 (13)	380 (13)	
2013	888 (13)	444 (15)		938 (14)	389 (14)	
2014	881 (13)	435 (15)		925 (13)	384 (13)	
2015	909 (13)	351 (12)		887 (13)	368 (13)	
2016	872 (13)	336 (12)		853 (12)	364 (13)	
2017	988 (14)	352 (12)		947 (14)	398 (14)	
2018	911 (13)	311 (11)		862 (13)	361 (13)	

The variables were summarized as mean ± SD or N (%). An absolute standardized difference value of greater than 0.10 indicates imbalance between the two groups.

Table 2. Subgroup Analysis by Surgery Type Demonstrating Mortality and Low Cardiac Output Syndrome by Morning and Afternoon Surgery and Odds Ratio of the Primary Composite Outcome (Morning *versus* Afternoon)

		Incidence of Mortality		Incidence of Low Cardiac Output Syndrome			
	N	Morning	Afternoon	Morning	Afternoon	Odds Ratio (95% CI)	*P* Value
Aortic valve replacement	2,657	0.3% (5 of 1,994)	0.8% (5 of 663)	1.3% (26 of 1994)	1.4% (9 of 663)	0.92 (0.48–1.76)	0.800
Aortic valve replacement + ascending aorta replacement	196	0 (0 of 145)	0 (0 of 51)	0 (0 of 145)	0 (0 of 51)		
Aortic valve replacement + coronary artery bypass grafting	854	0.7% (4 of 581)	0.4% (1 of 273)	2.8% (16 of 581)	3.7% (10 of 273)	0.86 (0.39–1.88)	0.697
Aortic valve replacement + coronary artery bypass grafting + other	181	1.6% (2 of 125)	5.4% (3 of 56)	12.0% (15 of 125)	14.3% (8 of 56)	0.72 (0.31–1.67)	0.444
Aortic valve replacement + mitral valve repair or mitral valve replacement	589	1.2% (5 of 424)	1.8% (3 of 165)	5.4% (23 of 424)	2.4% (4 of 165)	1.79 (0.74–4.34)	0.198
Coronary artery bypass grafting	1,121	0.6% (4 of 665)	0.4% (2 of 456)	1.5% (10 of 665)	2.4% (11 of 456)	0.84 (0.35–2.00)	0.690
Coronary artery bypass grafting + mitral valve repair	350	1.0% (2 of 199)	2.0% (3 of 151)	4.0% (8 of 199)	6.6% (10 of 151)	0.79 (0.31–2.07)	0.637
Coronary artery bypass grafting + mitral valve replacement	130	2.6% (2 of 78)	1.9% (1 of 52)	11.5% (9 of 78)	15.4% (8 of 52)	1.01 (0.34–3.02)	0.992
Mitral valve repair	2,956	0.05% (1 of 2136)	0.1% (1 of 820)	1.7% (37 of 2,136)	2.0% (16 of 820)	0.93 (0.52–1.67)	0.813
Mitral valve replacement	700	0.8% (4 of 512)	0.5% (1 of 188)	6.1% (31 of 512)	6.4% (12 of 188)	1.05 (0.54–2.03)	0.893

The values are adjusted for the potential confounding factors listed in table 1. The odds ratios are reported for afternoon *versus* morning.

surgery, subgroup analyses identified no substantive morning *versus* afternoon outcome differences across the entire cohort (n = 9,338) or within individual procedures including aortic valve replacement (n = 2,547). Our results are consistent with another analysis of patients having cardiac surgery, which similarly did not identify daytime variation in outcomes, although sample sizes were smaller, and procedure type was not considered.[5]

Our primary endpoint was a composite of in-hospital mortality and low cardiac output syndrome, and our data were restricted to in-hospital outcomes. We did not include postoperative myocardial infarction as an outcome because this term is only defined for patients having coronary artery bypass grafting.[24] In the prospective study by Montaigne *et al.*,[17] troponin T concentrations were lower following afternoon surgery. We could not conduct valid comparisons of troponin T concentrations because the biomarker was only evaluated on postoperative day 1 at a fixed time point (approximately 2:00 AM) for all patients, resulting in systematic differences in the time to blood sampling in morning and afternoon patients.

Table 3. Intraoperative and Postoperative Variables by Surgery Time

Variable	Morning (N = 6,859)	Afternoon (N = 2,875)
Intraoperative medications		
Epinephrine	2,805 (41)	1,298 (45)
Norepinephrine	3,280 (48)	1,350 (47)
Milrinone	369 (5)	197 (7)
Vasopressin	432 (6)	244 (8)
Propofol	6,206 (90)	2,610 (91)
Etomidate	4,897 (71)	2,088 (73)
Ketamine	68 (1)	23 (1)
Blood products		
Erythrocyte transfusion	1,061 (15)	552 (19)
Platelets transfusion	967 (14)	535 (19)
Fresh frozen plasma transfusion	480 (7)	270 (9)
Cryoprecipitate transfusion	244 (4)	142 (5)
Intensive care unit length of stay, days	2 (2, 3)	3 (2, 4)
Hospital length of stay, days	7 (6, 10)	8 (6, 10)

Variables are summarized as n (%) or median (quartile 1, quartile 3).

Although the incidence of the composite outcome did not differ significantly between morning and afternoon patients, the 95% CI spanned from a 25% reduction to a 24% increase in the odds for the outcome after morning surgery. The CIs were wide largely because the incidence of our primary composite outcome was low, and we were only adequately powered to test an odds ratio of 1.50. Nonetheless, the odds ratio was near 1.0, suggesting that in-hospital mortality and low cardiac output syndrome do not substantively differ for morning and afternoon aortic valve, mitral valve, and/or coronary artery bypass grafting surgeries. At the same time, the CI of the odds ratio (0.75 to 1.24) included a clinically important boundary, 1.20, indicating that the real difference might in fact be clinically meaningful.

Low cardiac output syndrome was defined by the need for two or more inotropic agents after cardiopulmonary bypass, a cardiac index of less than $2.0\ l \cdot min^{-1} \cdot m^{-2}$, documented left or right myocardial dysfunction, or documented cardiac insufficiency or cardiogenic shock postoperatively. Presumably, most patients experienced myocardial insufficiency/dysfunction consequent to cardioplegic arrest and

	Incidence of Mortality and/or Low Cardiac Output Syndrome	Adjusted Odds Ratio (95% CI)	P-Value
Morning vs. Afternoon *			**0.770**
Morning	2.8% (195/6859)	0.96 (0.75, 1.24)	
Afternoon	3.4% (97/2875)	Reference	
Morning vs. Afternoon by Surgery Type			
Aortic valve replacement	1.5% (41/2657)	0.92 (0.48, 1.76)	0.800
Aortic Valve replacement + Ascending Aorta	0% (0/196)	-	-
Aortic valve replacement + CABG	3.3% (28/854)	0.86 (0.39, 1.88)	0.697
Aortic valve replacement + CABG + Other	14.9% (27/181)	0.72 (0.31, 1.67)	0.444
Aortic + Mitral Valve Repair/Replacement	5.4% (32/589)	1.79 (0.74, 4.34)	0.198
Coronary Artery Bypass Grafting	2.1% (24/1121)	0.84 (0.35, 2.00)	0.690
CABG + Mitral Valve Repair	5.7% (20/350)	0.79 (0.31, 2.07)	0.637
CABG + Mitral Valve Replacement	14.6% (19/130)	1.01 (0.34, 3.02)	0.992
Mitral Valve Repair	1.8% (54/2956)	0.93 (0.52, 1.67)	0.813
Mitral Valve Replacement	6.7% (47/700)	1.05 (0.54, 2.03)	0.893
Aortic Cross-clamp Time by Hour			**0.989**
8 AM	1.8% (16/869)	Reference	
9 AM	2.2% (68/3157)	0.73 (0.41, 1.29)	
10 AM	3.9% (109/2796)	0.82 (0.47, 1.46)	
11 AM	5.7% (91/1606)	0.84 (0.46, 1.53)	
12 PM	7.1% (62/878)	0.84 (0.44, 1.58)	
1 PM	4.6% (32/701)	0.73 (0.37, 1.42)	
2 PM	3.5% (33/947)	0.78 (0.40, 1.49)	
3 PM	3.0% (34/1115)	0.78 (0.41, 1.47)	
4 PM	3.4% (27/802)	0.81 (0.41, 1.59)	
5 PM	4.7% (22/473)	0.92 (0.45, 1.90)	

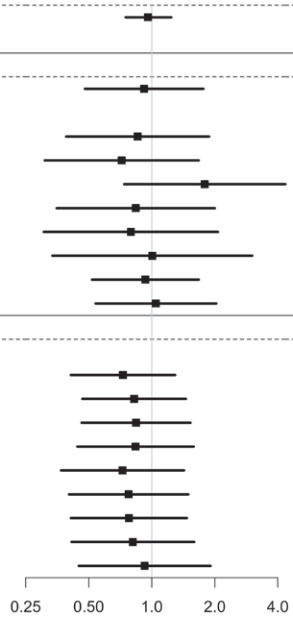

Fig. 2. Results of main analysis and sensitivity analyses. The incidence of the adjusted primary composite outcome, mortality and/or low cardiac output syndrome, is compared between patients who had morning *versus* afternoon surgery in all patients (primary analysis), by type of surgical procedure (sensitivity analysis), and by hour of aortic cross-clamp application (sensitivity analysis). *Morning surgery included those having aortic cross-clamp started between 8 and 11 AM, and afternoon surgery included those having aortic cross-clamp started between 2 and 5 PM.

ischemia–reperfusion injury, although we lacked elevated troponin concentrations or other data to prove this etiology.

Low cardiac output syndrome is a clinically meaningful outcome, with a specific definition.[22,25–27] There are limitations, however, related to the selection of this outcome. Our definition included the need for two or more inotropic medications at 24 to 48 h, which aims to identify patients who experience sustained myocardial dysfunction/failure after cardiac surgery. It is possible that inotropic agents were given for other reasons, such as right ventricular distention or fluid overload, although neither practice is routine at the Cleveland Clinic (Cleveland, Ohio). Importantly, our definition excludes patients who require only vasopressor therapy or "renal-dose" dopamine.

It is also possible that surgical complications including postoperative graft failure, surgical traumatic myocardial injury, or even cardiac dysfunction from cardiopulmonary bypass-induced systemic inflammatory response contributed to the development of low cardiac output syndrome. Although all patients required two or more inotropic agents at 1 to 2 days after surgery, our data show that these patients also received two or more inotropic agents intraoperatively, consistent with myocardial insufficiency caused by an intraoperative event rather than a postoperative complication, suggesting that the cause of low cardiac output syndrome was not acute postoperative graft occlusion. Cardiac dysfunction from a pronounced inflammatory response is also less likely because this condition often resolves within the first 24 h. Intraoperative cardiac dysfunction from aortic clamping and myocardial ischemia–reperfusion thus remains a likely explanation.

Other reports compared outcomes by time of day to assess whether factors such as availability of hospital resources or provider fatigue affected outcomes.[1,5] Our analysis could not distinguish between logistic factors, daytime variation in tolerance to myocardial ischemia, and other causes of low cardiac output syndrome. Nonrandom scheduling, variation in hospital resources such as intensive care unit bed availability, provider fatigue, and follow-up restricted to in-hospital period might all contribute to time-of-surgery outcome differences, although none was observed. Overall, it seems likely that what subtle time-of-day variations might exist are overwhelmed by other perioperative factors.

Investigating risk for cardiac complications and mortality associated with time of day was the primary purpose of this study, although a *post hoc* analysis was performed to examine other major Society of Thoracic Surgeons complications, including stroke, renal failure, deep sternal wound infection, cardiac reoperation, and prolonged ventilation. No differences in these outcomes were found, with the exception

of prolonged ventilation. We suspect that duration of ventilation was prolonged in afternoon surgery patients simply because those patients arrived late to the intensive care unit, and there was some reluctance to extubate at night.

Other limitations to our study include those inherent to its retrospective nature, most notably, the possibility of unmeasured confounders. All patients were cared for at a single quaternary care medical center with special expertise in cardiac care. The results might differ at smaller or less-experienced institutions, but it seems unlikely that institution-specific factors will make time of surgery an important factor. We were unable to examine the difference in troponin concentrations because of systematic differences in time to measurement. Pulmonary artery catheters are only used in about half of our patients, and thus cardiac index could not always be measured. Our analysis did not adjust for anesthesiologists, but the same anesthesia and surgical teams routinely managed both morning and afternoon cases. Furthermore, sensitivity analysis detected no difference by surgeon. Anesthesia medications were not included in the analysis, although the induction medications were similar in both groups. Atrial fibrillation was not included in the composite outcome because it is a less severe complication and occurs at a greater frequency than the other components of the composite and would heavily influence the result.[28] Finally, our analysis was restricted to in-hospital events because we did not have long-term outcomes postdischarge.

In summary, we found no evidence for time-of-day variation in mortality or low cardiac output syndrome in patients recovering from aortic valve surgery, mitral valve surgery, and/or coronary artery bypass grafting. Whereas there might be small time-of-day variations in outcome, they appear to be overwhelmed by other perioperative factors. Our results do not support selective morning or afternoon scheduling for cardiac surgery.

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Competing Interests

Dr. Duncan received funding from Fresenius Kabi (Bad Homburg, Germany) for research that is not relevant to the current article. Dr. Sessler is a consultant for Edwards Lifesciences (Irvine, California), Mercury Medical (Clearwater, Florida), Pacira (Parsippany, New Jersey), the Health Data Analytics Institute (Dedham, Massachusetts), and B. Braun (Melsungen, Germany). He serves on advisory boards and has equity interests in Calorint (Philadelphia, Pennsylvania), TransQtronics (Wilmington, Delaware), the Health Data Analytics Institute, Medasense (Ramat Gan, Israel), Serenno (Yokeneam Illit, Israel), and Sensifree (Cupertino, California). None is relevant to the current article. The other authors declare no competing interests.

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