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Is Nocturnal Extubation After Cardiac Surgery Associated With Worse Outcomes?

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Background. There is an increased risk of medical errors overnight compared with the day, secondary to fatigue, paucity of resources, and decreased staffing. Whether this increased risk extends to liberation from mechanical ventilation is controversial. We evaluated the relationship between length of intubation and differences between diurnal and nocturnal extubation.

Methods. We studied patients who had cardiac surgical procedures between January 1, 2007, and March 31, 2016, who were intubated on arrival to the cardiovascular intensive care unit (ICU) immediately after operation. Patients were divided into those extubated 24 or fewer hours or more than 24 hours after ICU arrival and were further divided by time of extubation: daytime (7 AM to 7 PM) and nocturnal (7 PM to 7 AM). We used multivariable logistic regression to determine whether nocturnal extubation was associated with increased mortality compared with diurnal extubation. Subgroup analyses investigated the effect of laboratory values, fluid management, and infused medicines.

Results. Two hundred seventy-eight of 8,705 patients (3.2%) died in the hospital; 84 died without being extubated. Of the remaining 8,621 patients, 6,982 patients (81%) were extubated within 24 hours of arrival to the ICU. Eighty-three of the patients (1.1%) died, and the proportion did not vary between day and night. In the delayed extubation group, 127 of the 1,639 patients (7.7%) died. Nocturnal extubation was associated with increased mortality only in the patients extubated more than 24 hours after ICU admission (adjusted odds ratio 2.46, 95% confidence interval: 1.45 to 4.16, $p = 0.001$). This increased risk persisted through all subgroup and sensitivity analyses.

Conclusions. Nocturnal extubation was associated with increased mortality only in the group of patients receiving more than 24 hours of mechanical ventilation.

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Several studies show that there is an increased risk of medical errors at night [1–4]. The house staff members are often working 24-hour shifts, and some studies show that these shifts are associated with more medical errors and almost twice as many attentional failures at night [2, 4]. The Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) trial, however, showed no outcome difference with standard versus less restrictive duty hours in surgery residents, and the Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education trial showed no statistically significant difference in the proportion of time spent between direct patient care and education in programs with standard policies of duty hour versus more flexible policies [5, 6]. Night shift nurses are often sleep deprived and have an increased rate of making errors in patient care [1, 3]. Furthermore, there is often decreased and less experienced staffing at night, and this could lead to decreased resources or lesser levels of experience [4]. There is conflicting evidence on whether a 24-hour intensivist model reduces mortality and morbidity for patients admitted to the intensive care unit (ICU) [7–9]. Banarjee and colleagues [8] found that 24-hour intensivist staffing reduced the length of stay and costs for the sickest patients admitted at night. However, a recent retrospective cohort of ICU patients by Costa and

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colleagues [9] found no difference in mortality and morbidity with 24-hour intensivist coverage.

Staffing patterns may also affect practice patterns [10]. Physicians may perform certain treatments and processes of care at night, or defer until daytime, based on patient severity of illness and perceived availability of resources [10, 11]. The conflicting data that exist for the risks of nocturnal extubation leads to the possibility that a select group of patients may benefit from avoidance of nocturnal extubation. Hickey and colleagues [12] showed in a review article of 14 studies on early endotracheal extubation in adult cardiac surgical patients that early extubation is safe, feasible, and desirable. The patient's medical condition, anesthetic technique, and surgical procedure are the major factors that determine whether a patient meets early extubation criteria [13]. Little information exists on the population of delayed extubation patients and the safety of nocturnal extubation for them. The objective of this study is to determine whether cardiac surgical patients have increased mortality if extubated at night and if it differs by duration of intubation. We hypothesize that patients extubated at night after cardiac operation have similar mortality as patients extubated during the day and that this does not vary between early and delayed extubation of patients.

Patients and Methods

This retrospective study was approved by the institutional review board, which waived informed consent. Patients were included if they had cardiac operation between January 1, 2007, and March 31, 2016, necessitating postoperative mechanical ventilation. Patients were excluded if they died before being extubated or were never extubated. Demographic data, comorbidities, type of operation, initial hours of mechanical ventilation, and perioperative mortality (defined as dying within 30 days of surgical procedure or longer if still hospitalized for the index operation) data were extracted from the institutional cardiac surgical database by using definitions from The Society of Thoracic Surgeons (STS). Additional data of perioperative fluids, postoperative infusions, and postoperative creatinine and hematocrit values were obtained from the electronic medical record. Because the perioperative electronic records were started later than the cardiac surgical database, we included these additional data in subgroup analyses. Sequential organ failure assessment score and STS predicted risk of mortality were calculated for all patients. Patients were divided into prompt (extubated within 24 hours of arrival in the ICU after operation) and delayed (extubated after 24 hours of arrival in the ICU after operation) extubation groups. We chose 24 hours as the dividing point based on the STS's definition of prolonged mechanical ventilation. To test if nocturnal extubation was associated with mortality, we divided all patients into daytime (7 AM to 7 PM) and nocturnal (7 PM to 7 AM) groups [13].

The staffing in the cardiovascular ICU at University of Michigan is with attending physicians, critical care fellows, anesthesiology residents, and nurse practitioners. During the night, there are anesthesiology residents and nurse practitioners in house, with fellows and attending physicians available by phone and who would come in if necessary. The registered nurse-to-patient ratio is similar between day and night. Most of the patients are staffed 1:1 and a few are 2:1. At least two respiratory therapists are dedicated to the unit both day and night. Patients typically undergo spontaneous breathing trials and are extubated if blood gases, arterial partial pressure of oxygen more than 60 mm Hg, arterial partial pressure of carbon dioxide less than 55 mm Hg, and mechanics such as respiratory rate (between 10 and 30 breaths/min), rapid shallow breathing index ($<$100 breaths $\cdot$ min^{-1} $\cdot$ L^{-1}), negative inspiratory force (less than $-$20 mm Hg), and vital capacity ($>$10 mL/kg) are acceptable.

Variables were compared by using Student's t test or Wilcoxon rank sum test for continuous variables, depending on normality, and Fisher's exact or χ^2 test for categorical variables. To determine the independent effect of extubation time on outcome, we used binary logistic regression models. Rare missing ($<$5% of patients) continuous data were imputed by using multiple imputation. Variables with more frequent missing data were binned, and the missing data were treated as a separate bin. Patients with off-pump surgical procedure were considered to have 0 minutes of cardiopulmonary bypass. We created four separate models that consisted of data from (1) institutional database that included demographic characteristics, comorbidities, and preoperative creatinine and hematocrit values; (2) addition of preextubation creatinine and hematocrit values; (3) further addition of intraoperative fluid intake and output; and (4) final addition of cumulative (from ICU arrival time to time of extubation) fluid intake and output, use of vasopressive or inotropic agents at extubation, and use of fentanyl and amiodarone infusions at extubation. Use of other infusions at time of extubation were rare and were excluded from analysis. Because we were concerned that some of the extubations would represent terminal extubations and might be more common in the evening, we did several sensitivity analyses to try to exclude these extubations, which are not captured in the database. Sensitivity analyses were done by restricting the delayed extubation group to include only patients extubated 336 or fewer hours (14 days) of initial postoperative ventilation, 96 or fewer hours of initial postoperative ventilation, and then by excluding patients who died within 4 hours of extubation. The 95% confidence interval that excluded 1 and p values less than 0.05 denoted statistical significance. SPSS version 24 (IBM, Chicago, IL) was used for all statistical analyses.

Results

From 2007 to 2016, 8,705 patients who underwent cardiac surgical procedures and were admitted to the

Table 1. Factors Associated With Perioperative Mortality in Patients Extubated Within 24 Hours After ICU Arrival

Factor	No.	Odds Ratio (95% CI)	*p* Value
Nocturnal extubation	…	1.36 (0.83–2.25)	0.226
Age, years	…	1.03 (1.01–1.05)	0.004
Chronic lung disease	…	2.17 (1.33–3.55)	0.002
Congestive heart failure	…	1.76 (1.03–3.01)	0.038
Ejection fraction	…	0.98 (0.97–0.997)	0.019
Preoperative hematocrit, %	…	0.96 (0.92–0.99)	0.024
Preoperative creatinine, mg/dL	…	1.19 (1.01–1.40)	0.041
Intraoperative RBC transfusion, unit	…	1.34 (1.21–1.48)	<0.001
Intraoperative platelet transfusion, unit	…	0.82 (0.69–0.98)	0.029
Other surgery	…	2.32 (1.12–4.81)	0.024
Peripheral vascular surgery	…	1.91 (1.04–3.51)	0.038
Constant	…	0.01	<0.001
Model			
1	6,982	1.36 (0.83–2.25)	0.226
2	6,689	1.38 (0.82–2.31)	0.222
3	5,978	1.29 (0.74–2.24)	0.365
4	2,253	1.10 (0.50–2.40)	0.813

Logistic regression models were created based on (1) institutional database and preoperative creatinine and hematocrit values; (2) addition of preextubation creatinine and hematocrit values; (3) further addition of intraoperative fluid intake and output; and (4) final addition of cumulative (from ICU arrival time to time of extubation) fluid intake and output, use of vasopressive or inotropic agents at extubation, and use of fentanyl and amiodarone infusions at extubation. C-statistic = 0.833 ± 0.020.

CI = confidence interval; ICU = intensive care unit; RBC = red blood cell.

cardiovascular ICU at the University of Michigan were included. Of the 8,705 patients, 278 patients (3.2%) died in hospital, 84 of them died without extubation, leaving 8,621 patients for analysis. Most, 6,982 (81%), of the remaining 8,621 patients were extubated within 24 hours of arrival to the ICU. Patients who were extubated within 24 hours were less likely to have comorbidities, had lower STS predicted mortality score and sequential organ failure assessment scores, and had lower creatinine values and higher hematocrit values. They were less likely to receive intraoperative blood transfusions and more likely to undergo coronary artery bypass grafting or valve operation (Supplemental Table 1). Only 83 patients (1.1%) extubated within 24 hours died. However, 127 of the 1,639 patients (7.7%) in the delayed extubation group died ($p < 0.001$).

Within both groups, patients who died were older, had more comorbidities, were more likely to receive transfusions, and have valvular operations (Supplemental Tables 2 and 3). While there was no increase in mortality in the nocturnally extubated patients in the prompt extubation group, patients extubated at night in the delayed extubation group were more likely to die (12% versus 7%, $p = 0.004$). After adjustment for confounders, we found that nocturnal extubation was not associated

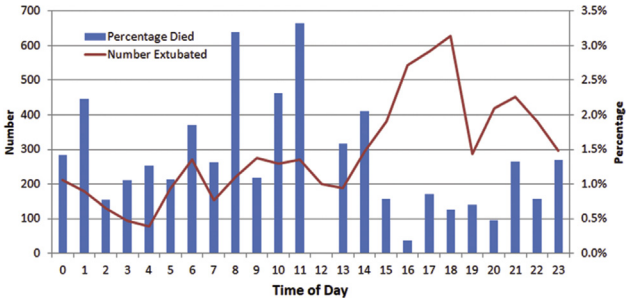

Fig 1. Percentage of patients who had been extubated within 24 hours who died.

with mortality in the prompt group (Table 1; Fig 1), whereas it was associated with more than a doubling of the odds ratio (OR) of dying in the delayed extubation group [adjusted OR (aOR) 2.46, 95% confidence interval (CI): 1.45 to 4.16, p 0.001] (Table 2; Fig 2).

When we did subgroup analyses, we found that there was no increased mortality in patients extubated at night in the promptly extubated group even when adjusted for creatinine and hematocrit values (n = 6,689, aOR 1.38, 95% CI: 0.82 to 2.31, $p = 0.222$); intraoperative fluid intake and output (n = 5,978, aOR 1.29, 95% CI: 0.74 to 2.24, $p = 0.365$); postoperative fluid intake and output and infusions of vasopressor agents, inotropic agents,

Table 2. Factors Associated With Perioperative Mortality in Patients Extubated After 24 Hours After ICU Arrival

Factor	No.	Odds Ratio (95% CI)	*p* Value
Nocturnal extubation	…	2.46 (1.45–4.16)	0.001
Age, years	…	1.02 (1.01–1.03)	0.007
Congestive heart failure	…	1.77 (1.12–2.81)	0.015
Intraoperative RBC transfusion unit	…	1.05 (1.01–1.09)	0.015
Intraoperative platelet transfusion, unit	…	1.06 (1.00–1.12)	0.050
Ejection fraction (0.01)	…	1.02 (1.01–1.03)	0.001
Valve surgery	…	1.95 (1.25–3.04)	0.003
Other surgery	…	2.08 (1.14–3.80)	0.017
Preoperative creatinine, mg/dL	…	1.16 (1.01–1.33)	0.035
Constant	…	0.01	<0.001
Model			
1	1,639	2.46 (1.45–4.16)	0.001
2	1,405	2.62 (1.54–4.46)	<0.001
3	1,211	2.46 (1.38–4.37)	0.002
4	1,197	2.96 (1.64–5.35)	<0.001

Logistic regression models were created based on (1) institutional database and preoperative creatinine and hematocrit values; (2) addition of preextubation creatinine and hematocrit values; (3) further addition of intraoperative fluid intake and output; and (4) final addition of cumulative (from ICU arrival time to time of extubation) fluid intake and output, use of vassopressive or inotropic agents at extubation, and use of fentanyl and amiodarone infusions at extubation. C-statistic = 0.679 ± 0.026.

CI = confidence interval; ICU = intensive care unit; RBC = red blood cell.

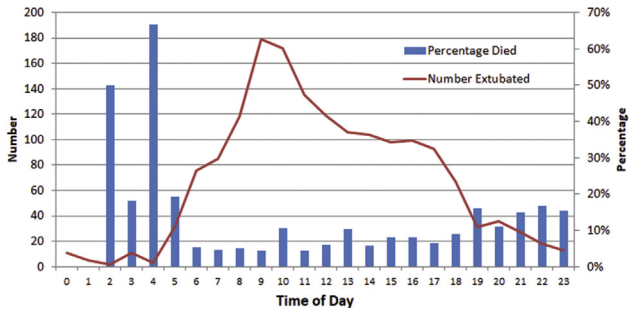

Fig 2. Percentage of patients who had been extubated after 24 hours who died.

fentanyl, and amiodarone (n = 2,253, aOR 1.10, 95% CI: 0.50 to 2.40, $p = 0.813$) (Table 1). In contrast, patients intubated for more than 24 hours after ICU admission had increased mortality in all three subgroup analyses. This association with increased risk of death remained present in the sensitivity analyses to exclude patients possibly extubated for palliative care created by excluding patients who remained intubated for more than 336 hours, more than 96 hours, or died within 4 hours of extubation (Supplemental Table 4).

Comment

Postoperative cardiac surgical patients who are extubated early have been shown to have shorter ICU and hospital stays, fewer resources consumed, and decreased morbidity [14, 15]. Extubation protocols are in place in many institutions that enable a quicker postoperative extubation. Although protocols may improve care for most patients, they may negatively affect individual patients. These measures may sometimes put patients at risk with extubation at night, which, with limited resources present, has been shown to increase mortality [7, 16].

We found that patients in the ICU extubated nocturnally who had been intubated for 24 or fewer hours after ICU admission have the same mortality as patients diurnally extubated. However, in patients in the ICU who have been intubated for more than 24 hours after ICU admission, nocturnal extubation was associated with an increased risk of death compared with diurnal extubation. This association remained after adjusting for other factors that may be associated with both delayed extubation and mortality. The results remained robust with various subgroup analyses, based on possible confounding factors that might also affect mortality rates, such as creatinine and hematocrit values, perioperative fluid intake and output, the use of vassopressive or inotropic agents, and the use of amiodarone or fentanyl.

Nationally, the rate of prolonged ventilation varies between cardiac surgical center and by type of operation [17–19]. Although the rate of prolonged ventilation is only 4.6% after mitral valve repair, it is 17.1% after mitral valve replacement and 28.1% after combined mitral valve replacement and coronary artery bypass grafting [19]. Given the approximately 300,000 cardiac operations performed annually and 10% prolonged ventilation rate, a doubling of mortality associated with nocturnal extubation would be associated with hundreds of excess deaths.

Previous studies have produced contradictory results about nocturnal versus diurnal extubation. Gershengorn and colleagues [16] reported that nocturnal extubation was associated with higher odds of ICU and hospital mortality than diurnal extubation. Contrarily, Tischenkel and colleagues [13] reported that patients who were extubated overnight had no change in mortality.

Although our findings of increased mortality in nocturnally extubated patients is similar to the study by Gershengorn and colleagues, our findings differ from their findings by showing that this increased mortality is only present in patients who have been intubated for at least 24 hours [16]. Unlike their study, which found an increase in mortality in patients intubated less than 12 hours who were extubated at night, we found no difference; cardiac patients nocturnally extubated after the operation had no increased mortality compared with patients diurnally extubated. Our differences in outcome may be related to different patient populations. We restricted our analysis to cardiac surgical patients, whereas their study included a variety of ICUs. Patient outcomes may differ by type of operation or presence or absence of operation.

Our findings differ from those of Tischenkel and colleagues [13], who found similar mortality rates between daytime and nighttime extubations. Our studies differ in that only one-half of their patients were cardiac surgical patients, whereas all our patients were. They further differ in that the ICUs in their study were staffed at night with an intensivist and a critical care fellow, whereas our ICU was staffed at night by residents and nurse practitioners. Recently, a retrospective before-and-after study found that 24/7 ICU coverage by intensivists decreased morbidity but not mortality in cardiac surgical patients [20]. Most importantly, Tischenkel and colleagues [13] did not evaluate the effect of duration of mechanical ventilation on daytime versus nighttime extubation. Because the majority (81%) of our patients were extubated within 24 hours of ICU admission, any increased mortality associated with nocturnal extubation might have been lost had we not analyzed duration of ventilation as separate groups. Further study is needed to better assess the role of nighttime intensivists, prolonged mechanical ventilation, and nocturnal extubation.

The lack of an attending intensivist or fellow overnight limits the senior experience at night, leading to decisions made by more junior members of the team. In 2017, a study of hospitalists found that less-experienced hospitalists had more adverse events than more experienced ones [21]. Our lower level of experience at night may, in part, explain the higher mortality of patients intubated for more than 24 hours who were extubated at night. However, this further emphasizes that, even without immediate senior experience overnight, there was no increased mortality in those patients who were extubated

at night if they had been mechanically ventilated for 24 or fewer hours. Thus, these patients are clearly able to do well regardless of the time of the day they were extubated.

In addition to the lack of senior members of the team overnight, there is an inherently increased rate of errors that occur overnight. Miller and colleagues [22] described a higher medication error rate for night shift nurses. Other studies describe similar findings in which the error rate on night shifts was consistently higher [23, 24]. Physicians are also affected by night work and sleep deprivation. Residents showed deterioration in psychomotor vigilance testing response times to both short- and long-term sleep deprivation [25]. In 2016, a study of 27 attending and 24 resident intensivists in three ICUs found that working memory capacity (11.3 ± 0.3 versus 9.4 ± 0.3, $p < 0.001$), speed of processing information (13.5 ± 0.4 versus 10.9 ± 0.3, $p < 0.001$), and perceptual reasoning (10.6 ± 0.3 versus 9.3 ± 0.3, $p < 0.002$) all worsened after a night of work [26]. This shows that all levels of staff may have increased cognitive delays during the nighttime hours, which may lead to more errors. The FIRST trial was published in 2016, and it compared standard with less restrictive duty hour policies for surgery residents. No statistically significant outcome difference was found in mortality, adverse outcomes, and resident well-being [5]. Although the study shows no change in standard versus restrictive resident duty hours on patient outcome, the study does not distinguish whether there are any changes in nocturnal versus diurnal outcomes. Further studies would need to be done to see whether either model carries a higher risk of nocturnal adverse outcomes or whether nocturnal outcomes are worse regardless of duty hour regulations. Makary and colleagues [27] described medical errors as being the third leading cause of death in the United States. Because there is a known increased rate of medical errors overnight, nocturnal extubations may play a part in this increased mortality [27]. Further study is needed to determine the reasons for this increased mortality and whether different staffing practices might mitigate this association.

Patients extubated in 24 or fewer hours may be less likely to have errors made because they have simpler operations that may require fewer clinical decisions [28, 29] and, hence, decreased opportunity for error. They also may be better able to tolerate clinical error, delayed clinical response, or a marginal extubation because they have fewer comorbidities and an increased reserve (Supplemental Table 1). The increased comorbidity level in patients extubated after 24 hours may make them more prone to worsening decompensation and harder to rescue once decompensation begins. The patients who have been intubated for more than 24 hours may also have critical illness myopathy or neuropathy, which predict failure to wean from the ventilator and may lead to statistically significant morbidity and mortality [30]. This would likely not affect those patients who were extubated in 24 or fewer hours of ICU admission, but it might have a role in the increased mortality of the prolonged intubation group [30].

Limitations of our study include that this was performed in a single academic center and in only cardiac surgical patients, which make the generalizability to other patient populations difficult. The study was also retrospective in nature, which makes it difficult to ascertain the decision-making process behind why patients were extubated at a given time. Because we did not have information on palliative or terminal extubations, we performed sensitivity analyses to try to control for possible palliative extubations, which in our practice, frequently occur in the afternoon or evening, after family and friends have had a chance to gather. These sensitivity analyses were done by restricting the delayed extubation group to include only patients extubated fewer than 336 hours of initial postoperative ventilation, fewer than 96 hours of initial ventilation, and then by excluding patients who died within 4 hours of extubation. Our finding of increased mortality in patients extubated at night remained present in these three sensitivity analyses, suggesting that terminal extubations were not the cause of the increased mortality. However, because we do not have information on terminal extubations and do not intubate orders, we cannot exclude that terminal extubations played a part in our findings and is a limitation of our study. Finally, we do not have information on causes of deaths or the complications and events that may have contributed to these deaths. Further study is needed to better understand why nocturnal extubation in patients intubated more than 24 hours after cardiac operation is associated with increased mortality.

In conclusion, we found that patients who are promptly extubated ($\leq$24 hours) after cardiac operation have the same mortality whether they are extubated during the day or at night. However, patients who require longer mechanical ventilation have an increased mortality if extubated between 7 PM and 7 AM.

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