ORIGINAL ARTICLE

Peri-intubation Cardiovascular Collapse in Patients Who Are Critically Ill

Insights from the INTUBE Study

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Abstract

Rationale: Cardiovascular instability/collapse is a common peri-intubation event in patients who are critically ill.

Objectives: To identify potentially modifiable variables associated with peri-intubation cardiovascular instability/collapse (i.e., systolic arterial pressure <65 mm Hg [once] or <90 mm Hg for >30 minutes; new/increased vasopressor requirement; fluid bolus >15 ml/kg, or cardiac arrest).

Methods: INTUBE (International Observational Study to Understand the Impact and Best Practices of Airway Management In Critically Ill Patients) was a multicenter prospective cohort study of patients who were critically ill and undergoing tracheal intubation in a convenience sample of 197 sites from 29 countries across five continents from October 1, 2018, to July 31, 2019.

Measurements and Main Results: A total of 2,760 patients were included in this analysis. Peri-intubation cardiovascular instability/collapse occurred in 1,199 out of 2,760 patients (43.4%). Variables associated with this event were older age (odds ratio [OR], 1.02; 95% confidence interval [CI], 1.02–1.03), higher heart rate (OR, 1.008; 95% CI, 1.004–1.012), lower systolic blood pressure (OR, 0.98; 95% CI, 0.98–0.99), lower oxygen saturation as measured by pulse oximetry/$F_{I_{O_2}}$ before induction (OR, 0.998; 95% CI, 0.997–0.999), and the use of propofol as an induction agent (OR, 1.28; 95% CI, 1.05–1.57). Patients with peri-intubation cardiovascular instability/collapse were at a higher risk of ICU mortality with an adjusted OR of 2.47 (95% CI, 1.72–3.55), $P < 0.001$. The inverse probability of treatment weighting method identified the use of propofol as the only factor independently associated with cardiovascular instability/collapse (OR, 1.23; 95% CI, 1.02–1.49). When administered before induction, vasopressors (OR, 1.33; 95% CI, 0.84–2.11) or fluid boluses (OR, 1.17; 95% CI, 0.96–1.44) did not reduce the incidence of cardiovascular instability/collapse.

Conclusions: Peri-intubation cardiovascular instability/collapse was associated with an increased risk of both ICU and 28-day mortality. The use of propofol for induction was identified as a modifiable intervention significantly associated with cardiovascular instability/collapse.

Clinical trial registered with clinicaltrials.gov (NCT03616054).

Keywords: intubation; cardiovascular collapse; airway management

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Tracheal intubation is one of the most high-risk and frequently performed procedures in patients who are critically ill. Cardiovascular adverse events are frequently observed after tracheal intubation, and different factors may play a role in the increased risk in patients who are critically ill compared with patients undergoing tracheal intubation to receive elective surgery. Underlying shock, hypoxemia, and acidosis may enhance the risk of severe hypotension, which, in turn, may be the consequence of positive pressure ventilation and/or induction agents (1, 2).

Drugs administered for induction may cause peri-intubation hypotension either through direct vasodilatory and negative inotropic effects or because of adrenergic response blunting (3, 4).

INTUBE (International Observational Study to Understand the Impact and Best Practices of Airway Management in Critically Ill Patients) enrolled 2,964 patients undergoing tracheal intubation in 197 sites from 29 countries worldwide. In this study, a high rate of cardiovascular events in the peri-intubation period has been reported. Of concern, patients experiencing peri-intubation hemodynamic instability were at a higher risk of 28-day mortality, highlighting the potential relevance of this event for patient morbidity and mortality (5). To date, the research agenda on interventions to reduce peri-intubation risk in critical care has mainly focused on peri-intubation oxygenation optimization and on methods to achieve intubation at the first attempt (6–13).

However, given the recognition of cardiovascular collapse as a key element of peri-intubation morbidity and mortality, the identification of modifiable variables associated with this event has a high priority to furthermore investigate interventions to mitigate its incidence and severity. Among modifiable factors, the pre-intubation administration of fluids, vasopressors, and the selected induction agent may have a major role in the incidence of cardiac arrest and hypotension after intubation, and these interventions have been rarely investigated to date (14, 15).

Our hypothesis was that peri-intubation cardiovascular instability/collapse has an impact on patient outcome and that modifiable patient and procedure-related variables may play a role and represent the target for risk reduction.

The aim of this nonprespecified secondary analysis of the INTUBE dataset was to report on the effect of peri-intubation cardiovascular instability/collapse on the outcome and investigate the factors independently associated with this event, with an emphasis on modifiable peri-intubation practices.

Methods

Study Design and Participants

The INTUBE study was a prospective cohort study conducted from October 1, 2018, to July 31, 2019, in 197 sites. Detailed information on study methods has been published elsewhere (5). The study was approved by the ethics committee of the coordinating center (Comitato Etico Brianza, No 1420 of July 31, 2018) and then by each local committee when required according to local regulations.

Briefly, each site enrolled all consecutive patients who were critically ill and undergoing in-hospital tracheal intubation during an 8-week period. Critically ill were defined as those patients with an underlying life-threatening condition causing cardio–respiratory failure or neurologic impairment. Patients undergoing intubation for the sole purpose of general anesthesia and patients intubated after a cardiac arrest and out-of-hospital were excluded. For this subanalysis, we also excluded patients with missing information for cardiovascular instability/collapse outcome calculation.

Centers were advised that an investigator not involved in the tracheal intubation procedure collected data on demographic and clinical characteristics, intubation setting, patient physiologic parameters before intubation, details of the tracheal intubation procedure, outcomes of the procedure, and status at ICU discharge.

Outcome Definition

The primary objective of this analysis was to identify modifiable variables associated with peri-intubation cardiovascular instability/collapse and the association of this event with patient outcomes. We defined cardiovascular instability/collapse as the occurrence of at least one of the following events occurring within 30 minutes from the start of the intubation procedure: systolic arterial pressure $<$65 mm Hg recorded at least once;

At a Glance Commentary

Scientific Knowledge on the Subject: Cardiovascular instability/collapse is a common peri-intubation event in patients who are critically ill, but the potentially modifiable variables associated with peri-intubation cardiovascular instability/collapse are not clear.

What This Study Adds to the Field?: Peri-intubation cardiovascular instability/collapse was associated with an increased risk of both ICU and 28-day mortality. The use of propofol for induction was identified as a modifiable intervention significantly associated with cardiovascular instability/collapse.

systolic arterial pressure <90 mm Hg for >30 minutes; new requirement for, or increase of vasopressors; fluid bolus >15 ml/kg to maintain the target blood pressure; or cardiac arrest (5, 15, 16).

We defined life-threatening cardiovascular collapse as the occurrence of either systolic blood pressure <65 mm Hg recorded at least once or cardiac arrest within 30 minutes from the start of the intubation procedure.

We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines for observational cohort studies (17).

Statistical Analysis

The characteristics of the cohort, overall and stratified by the presence of cardiovascular instability/collapse, were described through frequency and percentages if variables were categorical, through the median and interquartile range or mean and standard deviation if they were continuous. Univariable analyses were conducted through chi-square or Fisher exact test for categorical variables, through the Mann-Whitney or the *t* test for continuous variables.

We performed multivariable logistic regression models to evaluate the association between some clinically relevant baseline covariates and cardiovascular instability/collapse. We also performed a bivariable logistic regression model to evaluate the association of each component of the outcome of cardiovascular instability/collapse with the outcome of ICU mortality.

The inverse probability of treatment weighting (IPTW) method was applied to reduce the effects of confounding in analyzing the association between the treatment (i.e., use of vasopressors, fluid bolus, or propofol) and the outcome (i.e., cardiovascular instability/collapse) (18). First, a multivariable logistic regression model was performed to estimate the propensity score, which represents the probability of receiving a treatment depending on baseline patient characteristics. These were chosen among factors associated with both treatment and cardiovascular instability/collapse on the basis of clinical knowledge. Subsequently, the outcome of each patient was weighted by the inverse of the probability of the treatment received, creating a pseudopopulation in which the distribution of the measured baseline covariates was independent of the treatment. To avoid inaccurate weights for subjects with a very low probability of receiving the treatment, stabilized weights were used. In the pseudopopulation, measured confounders should be balanced between treatment groups. Therefore, standardized differences between treatment groups of all variables included in the model to estimate the propensity score were calculated and plotted. A standardized difference of less than 0.1 indicated a negligible difference in the mean or prevalence of a covariate between treatment groups. We finally performed a bivariable logistic regression model on the pseudopopulation to estimate the impact of each treatment on the risk of cardiovascular instability/collapse. To evaluate the impact of cardiovascular instability/collapse on ICU mortality and 28-day mortality, two multivariable logistic regression models adjusted for age, sex, heart failure, hematologic malignancy, ischemic heart disease, solid neoplasm, adjusted noncardiovascular SOFA (Sequential Organ Failure Assessment) score and noradrenaline infusion rate before intubation were performed. Noncardiovascular SOFA included all SOFA items except cardiovascular. Adjusted (noncardiovascular) SOFA score was adopted to account for some missing values on its items, and it was calculated as follows: (sum of the available items × 20)/([20 − 4] × number of missing items) (19, 20).

To account for clustering because of the presence of a site effect, these analyses were implemented using a mixed model with a random intercept for the site. All the regression models were implemented including patients with complete information for the variables included in the model (complete cases analysis). All *P* values were two-sided, with $P < 0.05$ considered statistically significant. Statistical analyses were performed with R software version 4.0.3 (http://www.R-project.org).

Results

Participating Centers and Enrolled Patients

A total of 197 active centers from 29 countries worldwide participated in the INTUBE study. Of the 3,659 screened patients, 2,964 patients were originally included. We excluded 94 intubations corresponding to reintubations of previously enrolled patients, and 204 patients were excluded because of missing information for the outcome of cardiovascular instability/collapse. A total of 2,760 patients were finally included in the current analysis (Figure 1).

The median age was 63 (interquartile range, 49–74) years and most patients were male (62.9%).

Patients had chronic arterial hypertension in 40.3%, ischemic heart disease in 14.6%, and heart failure (NYHA [New York Heart Association] score III or IV) in 9.35% of cases. The median SOFA score was 7.0 (interquartile range, 5.0–10), and the median oxygen saturation as measured by pulse oximetry (Sp_{O_2})/$F_{I_{O_2}}$ was 163 (interquartile range, 106–256). Seven hundred twenty-two (26.2%) patients were already receiving either a vasopressor or an inotropic drug before induction, and 1,030 (38.1%) patients received a fluid bolus before induction, with a median volume/weight of 7.14 ml/kg (interquartile range, 4.68–11.1 ml/kg) (Table 1).

Intubation Procedure and Induction Agents

Over two-thirds (67%) of intubations took place in the ICU, pre-oxygenation was by bag–valve–mask in 62%, and 62% were rapid sequence inductions. Further details

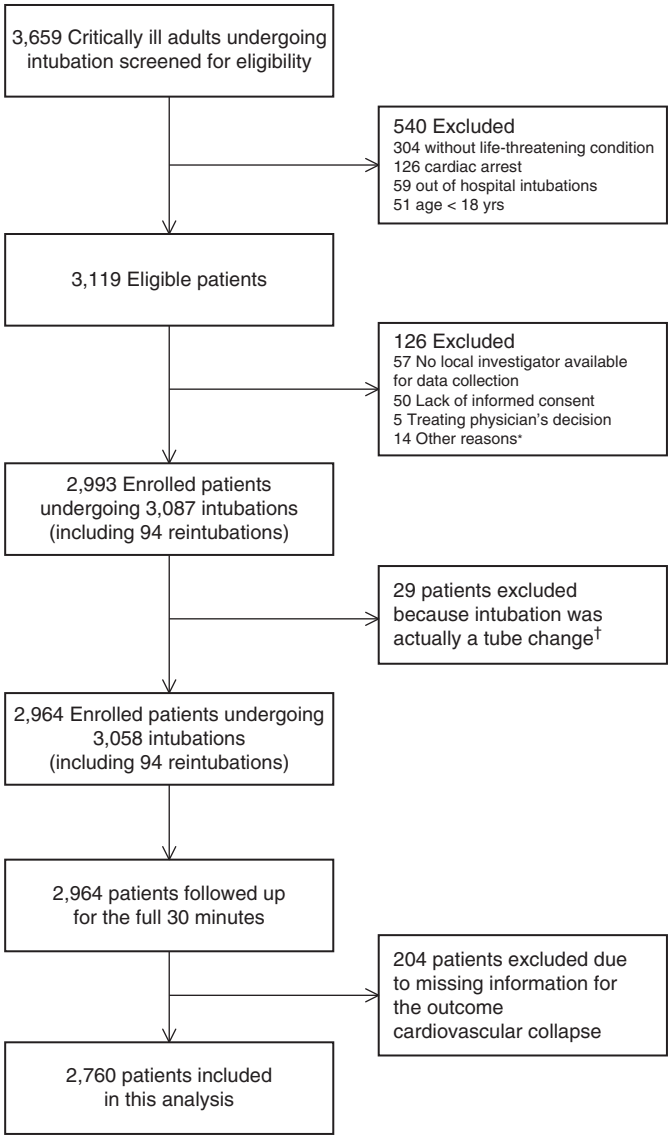

Figure 1. Study flow chart. *For these patients, reasons for exclusion were: situation too urgent for data collection in 10 patients, venoarterial extracorporeal membrane oxygenation in 2 patients, and prisoner status in 2 patients. †Patients were not reintubated but underwent tube change (e.g., for tube obstruction or cuff rupture) using a tracheal tube exchange catheter.

on the tracheal intubation setting are included in Table E1 in the online supplement, and a description of the procedure has been included in Table 2.

Propofol was the most commonly used induction agent, administered in 1,142 (41.4%) patients, with a median dose/weight of 1.12 (interquartile range, 0.71–1.67) mg/kg, followed by midazolam, used in 1,018 (36.9%) patients with a median dose/weight of 0.06 (interquartile range, 0.03–0.11) mg/kg, etomidate in 488 (17.7%) patients with a median dose/weight of 0.29 (interquartile range, 0.22–0.38) mg/kg, and ketamine in 398 (14.4%) patients with a median dose/weight of 1.28 (interquartile range, 0.82–1.82) mg/kg.

Propofol was more frequently used by anesthesiologists, who administered it in 743 (49.2%) patients, compared with nonanesthesiologists (i.e., emergency physicians and intensivists) who administered it in 399 (32.0%) patients, $P < 0.001$.

A muscle relaxant drug was administered in 1,962 (75.7%) patients, and rocuronium was the most used agent, administered in 1,167 (59.5%) of these patients.

Incidence of Cardiovascular Instability/Collapse

Cardiovascular instability/collapse occurred in 1,199 out of 2,760 (43.4%) patients.

Among these patients, 1,053 out of 1,199 (87.8%) required the initiation of a vasopressor after tracheal intubation or an increase of the infusion rate of an ongoing vasopressor; 253 out of 1,048 (24.0%) had a systolic blood pressure $<$90 mm Hg for $>$30 minutes after tracheal intubation; 157 out of 1,188 (13.2%) required a fluid bolus $>$15 ml/kg after intubation to maintain the target blood pressure; 151 out of 1,181 (12.8%) had a systolic blood pressure $<$65 mm Hg after intubation; and 93 out of 1,199 (7.8%) had a cardiac arrest within 30 minutes from intubation. Among patients with cardiac arrest, 52.7% had a sustained return of spontaneous circulation, while 47.3% of patients did not have a return of spontaneous circulation after the cardiac arrest.
A life-threatening cardiovascular collapse was reported in 228 out of 2,760 (8.3%) patients. Peri-procedural death was registered in 44 out of 2,760 (1.6%) patients.

On univariable analysis, a higher incidence of cardiovascular instability/collapse was observed in patients with ischemic heart disease and heart failure, in patients receiving noninvasive ventilation and apneic oxygenation, and in the 30–45° head-up position.

Figure 2 reports the systolic blood pressure drop after tracheal intubation for each quartile of baseline blood pressure in patients receiving or not receiving vasopressors or a fluid bolus before tracheal intubation and in patients receiving or not receiving propofol at induction. Notably, the higher the baseline systolic blood pressure, the higher the registered blood pressure drop after tracheal intubation.

ICU and 28-Day Mortality

Patients with peri-intubation cardiovascular instability/collapse were at higher risk of ICU mortality with an adjusted odds ratio (OR) of 2.47 (95% confidence interval [CI], 1.72–3.55); $P < 0.001$ (Table E2). Higher 28-day mortality was also observed, with an adjusted OR of 2.52 (95% CI, 1.72–3.68); $P < 0.001$ (Table E3).

Components of the composite outcome of cardiovascular instability/collapse significantly associated with increased ICU mortality were: vasopressors/fluids without hypotension (OR, 1.47; 95% CI, 1.21–1.79), systolic blood pressure $<$90 mm Hg for $>$30 min despite vasopressors (OR, 2.65;

Table 1. Demographic and Clinical Characteristics of Patients According to the Development of Cardiovascular Instability/Collapse After Intubation

Variable	Total (*N = 2,760*)	Cardiovascular Instability/Collapse (*n = 1,199*)	No Cardiovascular Instability/Collapse (*n = 1,561*)	*P* Value
Age, median (IQR), yr	63 (49–74)	66 (53–75)	61 (45–73)	<0.001
Sex, *n* (%)				0.18
Male	1,735 (62.9)	737 (61.5)	998 (63.9)	—
Female	1,025 (37.4)	462 (38.5)	563 (36.1)	—
BMI, median (IQR), kg/m^2	25.4 (22.5–29.4)	25.4 (22.4–29.4)	25.4 (22.5–29.3)	0.89
Arterial hypertension, *n* (%)	1,112 (40.3)	493 (41.1)	619 (39.7)	0.44
Diabetes, *n* (%)	671 (24.3)	296 (24.7)	375 (24.0)	0.69
Ischemic heart disease, *n* (%)	404 (14.6)	199 (16.6)	205 (13.1)	0.011
Heart failure (NYHA classification III– IV), *n* (%)	258 (9.4)	140 (11.7)	118 (7.6)	<0.001
SOFA score, median (IQR)*	7.0 (4.8–10.0)	8.0 (5.0–11.0)	6.0 (4.0–9.0)	<0.001
GCS, median (IQR) (*n = 2,754*)	10 (7–14)	11 (7–14)	10 (6–14)	0.30
Sp_{O_2}/FI_{O_2}, median (IQR) (*n = 2,205*)	163.3 (105.6–255.6)	153.3 (102.2–235)	180.4 (108.9–272.2)	<0.001
Receiving vasopressors/inotropic support, *n* (%)†	722 (26.2)	425 (35.4)	297 (19.0)	<0.001
Fluid bolus, *n* (%) (*n = 2,704*)‡	1,030 (38.1)	524 (45.5)	506 (32.6)	<0.001
Fluid volume, median (IQR), ml/kg (*n = 1,030*)	7.14 (4.68–11.1)	7.69 (5.42–13.2)	6.67 (3.77–9.24)	<0.001
Systolic blood pressure, mean (SD), mm Hg (*n = 2,757*)	126.0 (35.6)	113.6 (34.1)	135.5 (33.8)	<0.001
Diastolic blood pressure, mean (SD), mm Hg (*n = 2,757*)	69.8 (20.7)	63.2 (19.9)	74.9 (19.9)	<0.001
Heart rate, mean (SD), (*n = 2,757*)	103.7 (26.3)	105.5 (27.8)	102.3 (25.1)	0.002
Respiratory rate, mean (SD) (*n = 2,751*)	26.3 (10.0)	26.4 (9.9)	26.2 (10.1)	0.50
Reason for intubation, *n* (%) (*n = 2,757*)				<0.001
Respiratory failure	1,452 (52.7)	690 (57.7)	762 (48.8)	—
Neurological impairment	822 (29.8)	266 (22.2)	556 (35.6)	—
Cardiovascular instability	260 (9.4)	169 (14.1)	91 (5.8)	—
Airway obstruction	130 (4.7)	40 (3.3)	90 (5.8)	—
Degree of emergency, *n* (%) (*n = 2,758*)				0.24
Tracheal intubation required without any delay	1,436 (52.1)	614 (51.2)	822 (52.7)	—
Tracheal intubation required in <1 hr	979 (35.5)	445 (37.1)	534 (34.3)	—
Tracheal intubation required in ⩾1 hr	343 (12.4)	140 (11.7)	203 (13.0)	—
At least one anticipated anatomical difficult airway, *n* (%)				0.022
Yes	1,225 (44.4)	565 (47.1)	660 (42.3)	—
No	1,379 (50.0)	576 (48.0)	803 (51.4)	—
Not performed	156 (5.7)	58 (4.8)	98 (6.3)	—
MACOCHA score ⩾3, *n* (%)§	403 (14.6)	191 (15.9)	212 (13.6)	0.08

Definition of abbreviations: BMI = body mass index; GCS = Glasgow Coma Scale; IQR = interquartile range; MACOCHA = Mallampati score III or IV, obstructive sleep apnea syndrome, reduced mobility of cervical spine, limited mouth opening, coma, severe hypoxemia, and non-anesthesiologist operator; NYHA = New York Heart Association; SOFA = Sequentail Organ Failure Assessment; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

*Scores were calculated with the last values before intubation, and missing data omitted were adjusted accordingly.

†Vasopressors/inotrope started before induction.

‡Any fluid bolus was administered 30 minutes preceding intubation to reach or maintain the hemodynamic goals according to clinical judgment.

§Predicts difficult intubation in the ICU. Its calculation includes Mallampati score III and IV (5 points), obstructive sleep apnea syndrome (2 points), reduced mobility of the cervical spine (1 point), limited mouth opening <3 cm (1 point), coma (1 point), severe hypoxemia (1 point), nonanesthesiologist operator (1 point) (range: 0 = easy intubation; 12 = very difficult intubation) (37).

95% CI, 1.87–3.75), systolic blood pressure <65 mm Hg (OR, 1.89; 95% CI, 1.31–2.71), and cardiac arrest (OR, 8.79; 95% CI, 5.46–14.7) (Table E4 and Figure E1).

Multivariable Model on Variables Associated With Cardiovascular Instability/Collapse and Inverse Probability Weighting of Variables Before Intubation

In a multivariable model (Tables 3 and E5), variables significantly associated with peri-intubation cardiovascular instability/collapse were identified as follows: administration of propofol at induction (OR, 1.28; 95% CI, 1.05–1.57), older age (OR, 1.02; 95% CI, 1.02–1.03), higher heart rate before induction (OR, 1.01; 95% CI, 1.00–1.01), lower systolic blood pressure before induction (OR, 0.983; 95% CI, 0.980–0.987), and lower Sp_{O_2}/FI_{O_2} before induction (OR, 0.998; 95% CI, 0.980–0.987). In a second multivariable model (Table E6), variables significantly associated with peri-intubation life-threatening cardiovascular collapse were older age (OR, 1.03; 95% CI; 1.02–1.04), adjusted SOFA score (OR, 1.05; 95% CI, 1.001–1.10), lower systolic blood pressure before induction (OR, 0.987; 95% CI, 0.981–0.992), and lower Sp_{O_2}/FI_{O_2} before induction (OR, 0.998; 95% CI, 0.997–1.00).

To reduce the effect of confounding, we applied the IPTW method. In Figure E2, plots of the standardized differences between treatment groups for all variables included in

Table 2. Intubation Procedure and Operator Characteristics

Variable	Total (*N* = *2,760*)	Cardiovascular Instability/Collapse (*n* = *1,199*)	No Cardiovascular Instability/Collapse (*n* = *1,561*)	*P* Value
Preoxygenation method, *n* (%) (*n* = *2,756*)				0.010
Bag–valve–mask	1,725 (62.6)	746 (62.3)	979 (62.8)	—
Standard facemask	356 (12.9)	137 (11.4)	219 (14.1)	—
Noninvasive ventilation	324 (11.8)	166 (13.9)	158 (10.1)	—
High flow nasal cannula	145 (5.3)	70 (5.8)	75 (4.8)	—
Anesthesia breathing circuit	51 (1.9)	15 (1.3)	36 (2.3)	—
Continuous positive airway pressure	49 (1.8)	18 (1.5)	31 (2.0)	—
Venturi system	44 (1.6)	20 (1.7)	24 (1.5)	—
Nasal cannula	44 (1.6)	21 (1.8)	23 (1.5)	—
Apneic oxygenation, *n* (%) (*n* = *2,755*)	285 (10.3)	147 (12.3)	138 (8.9)	0.003
Rapid sequence induction, *n* (%) (*n* = *2,593*)	1,598 (61.6)	705 (63.3)	893 (60.4)	0.13
Patient position, *n* (%) (*n* = *2,757*)				0.001
Supine	1,760 (63.8)	725 (60.5)	1,035 (66.4)	—
30–45° head-up position	587 (21.3)	296 (24.7)	291 (18.7)	—
20° head-up position	265 (9.6)	115 (9.6)	150 (9.6)	—
Beach chair	63 (2.3)	22 (1.8)	41 (2.6)	—
Induction agent	2,589 (93.8)	1,113 (92.8)	1,476 (94.6)	0.06
Propofol, *n* (%)	1,142 (41.4)	460 (38.4)	682 (43.7)	0.005
Propofol dose/weight, median (IQR), mg/kg	1.12 (0.71–1.67)	1.05 (0.67–1.58)	1.18 (0.75–1.71)	0.003
Midazolam, *n* (%)	1,018 (36.9)	435 (36.3)	583 (37.3)	0.56
Midazolam, dose/weight, median (IQR), mg/kg	0.06 (0.03–0.11)	0.06 (0.03–0.11)	0.06 (0.03–0.11)	0.32
Etomidate, *n* (%)	488 (17.7)	224 (18.7)	264 (16.9)	0.23
Etomidate, dose/weight, median (IQR), mg/kg	0.29 (0.22–0.38)	0.29 (0.23–0.39)	0.29 (0.22–0.38)	0.52
Ketamine, *n* (%)	398 (14.4)	202 (16.8)	196 (12.6)	0.001
Ketamine, dose/weight, median (IQR), mg/kg	1.28 (0.82–1.82)	1.32 (0.85–1.82)	1.25 (0.80–1.79)	0.29
Muscle relaxant use, *n* (%) (*n* = *2,591*)	1,962 (75.7)	833 (74.8)	1,129 (76.4)	0.36
Rocuronioum	1,167 (42.3)	507 (42.3)	660 (42.3)	0.10
Succinylcholine	601 (21.8)	245 (20.4)	356 (22.8)	0.13
Opioid use, *n* (%) (*n* = *2,591*)	1,344 (51.9)	563 (50.6)	781 (52.8)	0.25
Elective method for laryngoscopy, *n* (%) (*n* = *2,759*)				0.024
Direct laryngoscopy with Macintosh or Miller blade	2,245 (81.4)	961 (80.2)	1,284 (82.3)	—
Videolaryngoscopy	478 (17.3)	228 (19.0)	250 (16.0)	—
Other	36 (1.3)	10 (0.8)	26 (1.7)	—
Intubation adjunct, *n* (%) (*n* = *995*)				0.3
Stylet	769 (77.3)	334 (79.1)	435 (75.9)	—
Bougie	217 (21.8)	86 (20.4)	131 (22.9)	—
Other	9 (0.9)	2 (0.5)	7 (1.2)	—
Intubation at first attempt, *n* (%) (*n* = *2,754*)	2,204 (80.0)	950 (79.4)	1,254 (80.5)	0.49
Operator performing the first attempt, *n* (%) (*n* = *2,758*)				0.39
Resident	1,458 (52.9)	618 (51.6)	840 (53.8)	—
Staff physician/consultant	834 (30.2)	369 (30.8)	465 (29.8)	—
Fellow	384 (13.9)	178 (14.9)	206 (13.2)	—
Medical student	63 (2.3)	23 (1.9)	40 (2.6)	—
Other	19 (0.7)	10 (0.8)	9 (0.6)	—
Field of training of the operator performing the first attempt, *n* (%) (*n* = *2,758*)				0.011
Anesthesia	1,511 (54.8)	652 (54.4)	859 (55.1)	—
Critical care/intensive care	621 (22.5)	287 (24.0)	334 (21.4)	—
Emergency medicine	299 (10.8)	109 (9.1)	190 (12.2)	—
Internal medicine	126 (4.6)	54 (4.5)	72 (4.6)	—
Pulmonary and critical care medicine	98 (3.6)	55 (4.6)	43 (2.8)	—
Other	103 (3.7)	41 (3.4)	62 (4.0)	—

Definition of abbreviation: IQR = interquartile range.

the model to estimate the propensity score were displayed. After using the IPTW method, the covariates were balanced across treatment groups. From the three different bivariable logistic regression models estimated on the pseudopopulation weighted for the propensity score, we found that the only treatment with a significant impact on cardiovascular instability/collapse was the use of propofol (OR, 1.23; 95% CI, 1.02–1.49) as an induction agent. The use of vasopressors (OR, 1.33; 95% CI, 0.84–2.11) or fluid boluses (OR, 1.17; 95% CI, 0.96–1.44) before induction was not significantly associated with cardiovascular instability/collapse.

The administered dose of propofol, standardized for the weight of each patient,

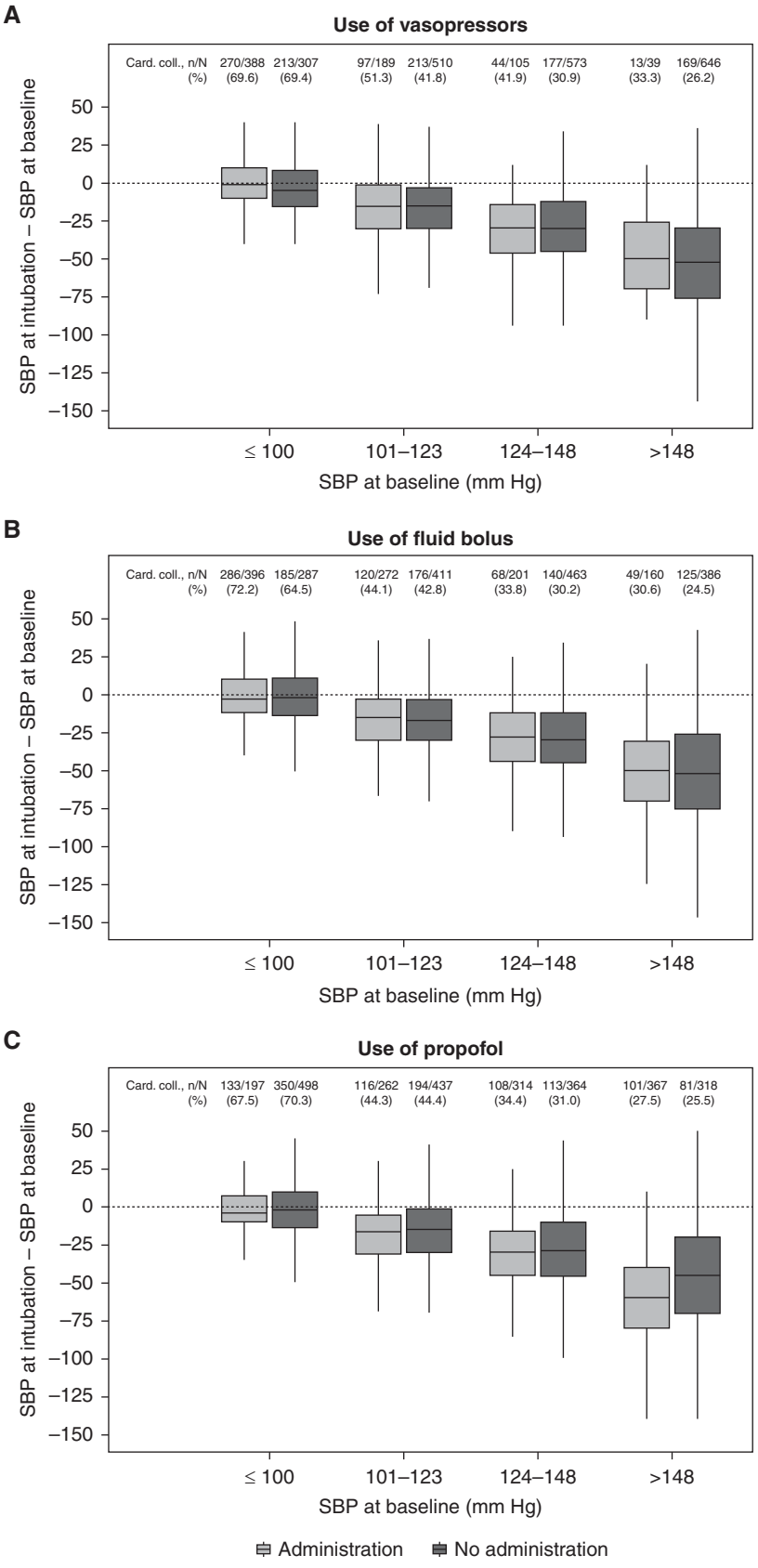

Figure 2. SBP drops after tracheal intubation as a function of SBP at baseline and treatment. Baseline blood pressure is categorized in quartiles, and the drop after tracheal intubation is represented in each quartile separately in patients receiving or not receiving

Table 3. Effect of Vasopressors, Fluid Bolus, Use of Propofol, Age, Adjusted Sequential Organ Failure Assessment Score, Heart Rate, Oxygen Saturation as Measured by Pulse Oximetry/FI_{O_2}, Systolic Blood Pressure on Cardiovascular Instability/Collapse by a Multiple Logistic Regression Model

Variable	OR	(95% CI)	*P* value
Vasopressors	1.143	(0.854–1.530)	0.37
Fluid bolus	1.187	(0.962–1.464)	0.11
Use of propofol	1.283	(1.047–1.572)	0.016
Age (yr)	1.022	(1.016–1.028)	<0.001
Adjusted SOFA	1.024	(0.995–1.053)	0.101
Heart rate	1.008	(1.004–1.012)	<0.001
Sp_{O_2}/FI_{O_2}	0.998	(0.997–0.999)	<0.001
Systolic blood pressure (mm Hg)	0.983	(0.980–0.987)	<0.001

Definition of abbreviations: CI = confidence interval; OR = odds ratio; SOFA = Sequential Organ Failure Assessment; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

was included in the model estimated on the pseudopopulation. Despite a statistically significant association of propofol use with cardiovascular instability/collapse (OR, 1.39; 95% CI, 1.02–1.90), propofol dosage does not have a significant association with cardiovascular instability (OR, 0.91; 95% CI, 0.74–1.10). We applied the IPTW method to identify variables associated with peri-intubation life-threatening cardiovascular collapse. Neither vasopressors use (OR, 0.89; 95% CI, 0.48–1.65) nor fluid boluses before induction (OR, 1.07; 95% CI, 0.74–1.53) nor propofol use (OR, 1.02; 95% CI, 0.72–1.46) were significantly associated with life-threatening cardiovascular collapse.

Discussion

In this large international cohort study, peri-intubation cardiovascular instability/collapse occurred in 43.4% of patients, and it was associated with an increased risk of both ICU and 28-day mortality. Propofol, which was frequently administered at intubation, was significantly associated with a higher risk of cardiovascular instability, but it was not associated with life-threatening collapse. This is the first large international cohort study to identify a modifiable factor independently associated with the hemodynamic changes in patients who were critically ill and undergoing tracheal intubation or to assess the impact of these changes on mortality.

Our findings support and extend those previously published by Halliday and colleagues, who performed a secondary analysis of a pooled dataset from three randomized trials to identify factors associated with peri-intubation cardiovascular collapse, with older age, lower systolic blood pressure and saturation at induction, and propofol use among variables associated with an increased risk of events while cirrhosis being interestingly associated with a reduced risk (21). These findings were mostly concordant with those from the present cohort, in which older age, lower pre-intubation systolic blood pressure, lower Sp_{O_2}/FI_{O_2}, and propofol use were also associated with an increased risk of events. While the prevalence of cirrhosis was not collected in our cohort, chronic liver failure was not significantly associated with the risk of cardiovascular instability at univariable analysis.

While interventions to optimize peri-intubation oxygenation have been largely investigated in patients who are critically ill (11, 22–24), strategies to optimize peri-intubation hemodynamics have been rarely assessed in randomized studies to date.

In a pre–post study conducted in three French ICUs, the implementation of an intubation bundle was associated with a lower incidence of peri-intubation adverse events compared with the baseline period. The 10-item bundle included the presence of two operators, preoxygenation with positive pressure ventilation, fluid loading with 500 ml of saline, induction with either ketamine or etomidate, and early start of noradrenaline (after intubation) in case of persisting diastolic pressure <35 mm Hg (14). Severe hypoxemia and cardiovascular instability, which were the two major peri-intubation adverse events, were reduced by half after implementing this bundle compared with the control period. However, it was not possible to ascertain which intervention in the bundle was more effective at reducing the risk of peri-intubation cardiovascular instability (14).

In the Preventing Cardiovascular collaPse With Administration of Fluid Resuscitation Before Endotracheal Intubation (PREPARE) trial conducted in nine sites in the United States, adult patients who were critically ill and undergoing tracheal intubation were randomized to receive either 500 ml of a crystalloid solution or no fluid bolus. The trial was interrupted for futility after detecting the lack of benefit of the crystalloid bolus on hemodynamic collapse after intubation (15). In the present study, no association was found between the use of a fluid bolus or vasopressors and the risk of peri-intubation cardiovascular instability/collapse. However, patients receiving vasopressors before intubation may have been deemed at higher risk of cardiovascular collapse after intubation, and the use of vasopressors in these patients may have offset this risk.

Induction agents may have a major influence on hemodynamic status after intubation (25–27), while peri-intubation vasopressors may counterbalance the vasodilatory effects of these induction agents and prevent peri-intubation cardiovascular instability/collapse. However, their use as a preemptive strategy has never been investigated during the peri-intubation period in patients who are critically ill.

In a multicenter French study, patients who were critically ill and undergoing rapid sequence induction were randomized to

Figure 2. (*Continued*). vasopressors or a fluid bolus before intubation and in patients receiving or not receiving propofol at induction. In the top row, the incidence of the composite outcome of cardiovascular instability/collapse in each quartile of baseline blood pressure. From the decreasing behavior of the boxplots, we may observe that the higher the baseline SBP, the higher the registered blood pressure drop after intubation. Card. Coll. = cardiovascular collapse; SBP = systolic blood pressure.

receive either etomidate or ketamine. Although a significantly higher rate of adrenal insufficiency was detected in the etomidate group, no significant differences were detected in patient morbidity and mortality in the two groups (28).

Guidelines on airway management in the critically ill suggest ketamine or etomidate as preferred induction agents because of their more favorable hemodynamic profile (29–31). Interestingly, the INTUBE study showed that approximately 40% of patients who were critically ill received propofol at induction, while etomidate and ketamine were used in only 18% and 14% of patients, respectively (5). After induction, propofol may be associated with hypotension by means of decreased myocardial contractility, venous dilation with a decreased venous return, and arterial dilation with a decrease in systemic vascular resistance (32, 33).

These effects are more pronounced in elderly and hypovolemic patients, patients with a reduced cardiovascular reserve, and the critically ill. Moreover, an association has been identified between infusion rate at the induction and after hypotension in patients aged 60 years or older (34).

In a single-center retrospective study of trauma patients intubated in a U.S. emergency department, propofol use was significantly associated with hypotension after intubation. The authors did not observe a dose–response relationship, indicating that adverse hemodynamic effects are observed at any propofol dosage (3). Interestingly, also in the current study, we reported the lack of an association between propofol dose and peri-intubation cardiovascular instability/collapse. This may indicate that in patients who are critically ill, even low doses of propofol, often administered in association with other hypnotics and opioids, may play a relevant role in hemodynamic instability.

In a multicenter observational study including adult and pediatric ICUs and emergency departments in the United States, significant heterogeneity of practice was detected according to the specialty of different providers. Indeed, emergency medicine providers more often used etomidate and ketamine than providers with a background in anesthesia, who more frequently used propofol as an induction agent (35). This was also observed in this study, in which anesthesiologists more frequently used propofol for induction than providers with a different training background (i.e., emergency medicine and intensive care), possibly for the familiarity acquired in the operating room. Patients who are critically ill, however, are at higher risk of developing the adverse cardiovascular effects of propofol than patients undergoing general anesthesia for surgery (3). Notably, a more severe drop of systolic blood pressure was registered in patients with baseline higher values, which may be the consequence of a higher amount of sympathetic activation, which may induce a false sense of safety at the moment of induction and the selection of agents, such as propofol, with a more hypotensive effect. Although of observational nature, the results of this study suggest the avoidance of propofol as the first choice for induction of patients who are critically ill, considering the availability of agents with a more favorable hemodynamic profile (e.g., ketamine and etomidate) (10, 29).

Clinicians dealing with airway management of patients who are critically ill should be aware of the high risk of peri-intubation cardiovascular instability/collapse and consider measures to optimize hemodynamic status when feasible. In addition, careful consideration should be given to the use of propofol, even at low dosages, given its association with peri-intubation cardiovascular instability.

Limitations

This study has several limitations. First, in 88% of patients, the classification of hemodynamic instability was on the basis of the initiation or increase in vasopressor; therefore, the outcome definition relied on a subjective clinical decision rather than objective hemodynamic data. However, in a real-life scenario of patients who are critically ill, clinicians either prevent or promptly react to hypotension with vasopressors, but these patients were at increased risk of ICU mortality despite blood pressure maintained within normal range. In addition, it should be acknowledged that there is not a consensus definition of the outcome of peri-intubation cardiovascular instability/collapse and that the definition adopted in this study combined elements of previously published definitions (5, 15, 16). However, we consider the definition adopted in this study of clinical value and consistent with these previously published studies.

Second, in approximately 7% of patients, data for the outcome calculation were missing. Although this represents a relatively small proportion of the whole cohort of patients, this may have influenced the results. Third, in this cohort, propofol was frequently administered with different combinations of induction drugs and/or opioids whose contribution to peri-intubation cardiovascular collapse cannot be excluded. However, this study has the merit of describing the extensive use of propofol for intubation in a large international cohort of patients who are critically ill and the association of this drug with cardiovascular collapse after intubation. Fourth, similarly to other large observational studies, direct verification of source data was not possible (36). Fifth, a selection bias of participating centers may have occurred. However, this is the largest prospective study investigating airway management in patients who are critically ill with a representation of different geographical areas and degrees of care. Sixth, although we adopted different adjustment methods, residual confounders may have influenced the incidence of cardiovascular instability/collapse in specific subgroups of patients who are critically ill, and the observational nature of the data does not enable us to infer causation. Finally, we did not collect information on the long-term consequences of the peri-intubation cardiovascular instability/collapse (e.g., myocardial injury and acute kidney injury). However, we identified an association between peri-intubation cardiovascular instability/collapse and ICU and 28-day mortality, which may indicate a meaningful role in patient morbidity and mortality and implications for clinical practice.

Conclusions

Peri-intubation cardiovascular instability/collapse was frequent in patients who were critically ill, and it was associated with an increased risk of both ICU and 28-day mortality. After correction for measured confounders, the use of propofol for induction was identified as a modifiable intervention significantly associated with cardiovascular instability/collapse. ■

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