Risk Factors for Cardiovascular Collapse during Tracheal Intubation of Critically Ill Adults

To the Editor:

Tracheal intubation is a high-risk procedure in critically ill adults, and 20–25% of patients experience cardiovascular collapse, defined as hypotension, new vasopressor use, cardiac arrest, or death during or immediately after the procedure (1–3). Despite the high prevalence of this complication, relatively little is known about risk factors for cardiovascular collapse during tracheal intubation, and no reliable prediction model exists for this outcome (2–4). In this secondary analysis of data from three large, pragmatic trials in airway management, we developed and validated a prediction model for cardiovascular collapse for use in analyzing heterogeneity of treatment effect and for prognostic enrichment in trials evaluating interventions to prevent cardiovascular collapse during tracheal intubation of critically ill adults (1, 5–8).

Methods

We performed a secondary analysis of data from the PrePARE (Preventing Cardiovascular Collapse with Administration of Fluid Resuscitation before Endotracheal Intubation), PreVent (Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation), and Check-UP (Checklists and Upright Positioning in Endotracheal Intubation of Critically Ill Patients) trials, which examined fluid bolus administration, bag-mask ventilation, and ramped positioning, respectively, during tracheal intubation of critically ill adults (1, 5, 6, 8). In each of these trials, any adult undergoing tracheal intubation in a participating intensive care unit (ICU) or emergency department was eligible, unless they were believed to have a specific contraindication to the study intervention or unless the procedure was too emergent to obtain a randomization envelope. The Vanderbilt Institutional Review Board (160158) approved this analysis.

Cardiovascular collapse was defined, as in previous trials, as a new systolic blood pressure (SBP) <65 mm Hg or new or increased vasopressor administration between induction and 2 minutes after intubation or cardiac arrest or death within 1 hour of intubation (1). Patients were excluded from this analysis if the indication for intubation was cardiac arrest or if the SBP at induction was <65 mm Hg. Predictor variables were selected on the basis of prior literature, clinical knowledge, and consistent data collection across trials (2–4, 9, 10). Twenty candidate variables were selected *a priori*, which are shown in Table 1. An elastic net logistic regression model, which combines ridge and lasso regression coefficient penalties to avoid overfitting, was trained using data from the PrePARE and PreVent trials. Five repeats of 10-fold cross-validation were used to choose the hyperparameters (i.e., ridge and lasso penalty term values) that maximized the area under the receiver operating characteristic curve (AUC) in the training dataset. Restricted cubic splines were used to test for nonlinearity of the continuous variables to determine if this improved accuracy during cross-validation. The model was then externally validated with data from the Check-UP trial, using the AUC for model discrimination and the unreliability index for calibration (11, 12). All analyses were performed using Stata version 16.0 software (StataCorp) and R version 3.6.1 software (R Foundation for Statistical Computing).

Results

A total of 815 patients were included in the analysis, with 109 events in 529 patients in PreVent and PrePARE and 58 events in 286 patients in Check-UP. Differences in characteristics between the training and validation cohorts are shown in Table 1.

The final elastic net prediction model derived in the PrePARE/PreVent trials excluded 5 of the 20 possible predictor variables and had an AUC of 0.74 (95% confidence interval [CI], 0.67 to 0.81) in the Check-UP trial. Restricted cubic splines did not improve model discrimination in the training dataset and were not included in the final model. Figure 1 shows a variable importance plot for this model, which illustrates which variables contributed the most to model predictions on a 0–100 scale by using the absolute value of the variable coefficients and then scaling to a maximum value of 100. The model was well calibrated with a calibration intercept of −0.05 (95% CI, −0.35 to 0.26), a calibration slope of 0.99 (95% CI, 0.63 to 1.37), and an unreliability index of $P = 0.96$ (Figure 2).

Several variables were significantly different between the training and validation cohorts, including age, sex, prevalence of chronic heart disease, SBP before intubation, and selection of induction and paralytic agents (Table 1). The most important predictors of cardiovascular collapse in the combined dataset, as determined by the elastic net regression model, were SBP at induction, preintubation vasopressors, age, and cirrhosis (Figure 1).

Discussion

In this secondary analysis of data from three large, pragmatic trials, we developed a model with moderate discrimination for predicting cardiovascular collapse during tracheal intubation in critically ill adults. Accurately quantifying patients' baseline risk of an outcome is fundamental to addressing patient heterogeneity in critical care clinical research (13). Our model predicting cardiovascular collapse may be used to analyze heterogeneity of

Supported in part by the Arthur P. and Lisa Wheeler Scholarship Research Grant (J.D.C.). The clinical trials on which this secondary analysis is based used the Research Electronic Data Capture (REDCap) tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from the National Center for Advancing Translational Sciences/National Institutes of Health). J.D.C. was supported in part by the U.S. National Heart, Lung, and Blood Institute (grant K12HL133117). M.W.S. was supported in part by the National Heart, Lung, and Blood Institute (grant K23HL143053). M.M.C. is supported in part by the National Institute of General Medical Sciences (grant R01 GM123193). The funding institutions had no role in *1*) conception, design, or conduct of the study; *2*) collection, management, analysis, interpretation, or presentation of the data; or *3*) preparation, review, or approval of the manuscript.

Author Contributions: S.J.H. designed the study, participated in the analysis, and prepared the manuscript. J.D.C., T.W.R., and M.W.S. designed the study, managed the database, participated in the analysis, and revised the manuscript. D.R.J., D.W.R., J.D., D.J.V., and J.R.W. collected data and revised the manuscript. M.M.C. designed the study, performed the analysis, and prepared the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Table 1. Demographics and baseline characteristics of the study population

	Combined Cohort (*N* = 815)	PrePARE/PreVent (*n* = 529)	Check-UP (*n* = 286)
Age, yr	59 (47–68)	60 (48–69)	57 (47–66)
Sex, F	328 (40.2%)	225 (42.5%)	103 (36.0%)
Body mass index, kg/m^2	27.2 (23.2–32.8)	27.3 (22.8–32.8)	27.1 (23.9–32.8)
Comorbidities			
Cardiac (congestive heart failure or atrial fibrillation)	196 (24.1%)	146 (27.6%)	50 (17.5%)
Chronic renal disease*	129 (15.8%)	88 (16.6%)	41 (14.3%)
Cirrhosis	151 (18.5%)	95 (18.0%)	56 (19.6%)
Oxygen saturation before tracheal intubation	99% (96–100%)	99% (96–100%)	99% (95–100%)
Systolic blood pressure before tracheal intubation, mm Hg	123 (106–142)	124 (107–144)	119 (102–142)
Receipt of vasopressors in 6 h before tracheal intubation	152 (18.7%)	97 (18.4%)	55 (19.2%)
APACHE II score	21 (16–27)	21 (16–28)	22 (18–26)
Indication for tracheal intubation†			
Hypoxic respiratory failure	466 (57.2%)	306 (57.8%)	160 (55.9%)
Hypercarbic respiratory failure	157 (19.3%)	109 (20.6%)	48 (16.8%)
Neurologic (e.g., depressed mental status, airway protection, seizure, agitation)	312 (38.3%)	204 (38.6%)	108 (37.8%)
Facilitate procedure	90 (11.0%)	54 (10.2%)	36 (12.6%)
Induction agents for tracheal intubation‡			
Etomidate	661 (81.1%)	416 (78.6%)	245 (85.7%)
Propofol	101 (12.4%)	79 (14.9%)	22 (7.7%)
Benzodiazepine	57 (7.0%)	49 (9.3%)	8 (2.8%)
Ketamine§	67 (8.2%)	40 (7.6%)	27 (9.4%)
Neuromuscular blockade during tracheal intubation			
Succinylcholine	333 (40.9%)	198 (37.4%)	135 (47.2%)
Nondepolarizing agent	450 (55.2%)	305 (57.7%)	145 (50.7%)

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; Check-UP = Checklists and Upright Positioning in Endotracheal Intubation of Critically Ill Patients; PrePARE = Preventing Cardiovascular Collapse with Administration of Fluid Resuscitation before Endotracheal Intubation; PreVent = Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation.
Data are presented as median (interquartile range) or count (percent).
*Includes chronic kidney disease and end-stage renal disease.
†Indications are not mutually exclusive, and subjects may have had more than one indication selected.
‡Subjects may have received more than one induction agent.
§Includes 62 patients who received ketamine, 3 patients who received lidocaine, and 2 with induction agent marked as "other."

treatment effect in ongoing trials evaluating interventions to prevent cardiovascular collapse during tracheal intubation of critically ill adults (NCT03787732). In addition, the risk factors identified may be used to selectively enroll patients at high risk of cardiovascular collapse in future trials.

Of the variables tested, SBP at induction, preintubation vasopressors, and age were important independent predictors of cardiovascular collapse. These results are not surprising, but our model helps to quantify the relative degree to which these factors influence risk for cardiovascular collapse. Comorbid cirrhosis, surprisingly, was associated with a reduced risk of cardiovascular collapse. It is uncertain whether this represents differences in the reasons for which patients with cirrhosis undergo intubation, differences in clinician management of vasopressors for this group with chronic vasodilation, or another reason. Choice of induction and paralytic agent, although debated clinically, had little association with risk for cardiovascular collapse in the overall model.

Our study has several strengths: use of high-quality data from clinical trials; validation of the model in an external cohort; and use of a robust, unified statistical approach to perform both variable selection and coefficient estimation. The study also has several weaknesses. Data were derived from a limited number of ICUs in the United States, and the results may not be generalizable to other settings. Cardiovascular collapse is a composite outcome; patients and providers do not perceive low SBP and vasopressor receipt to be equivalent to cardiac arrest and death, and the criteria for vasopressor administration were not predefined in the trials. Because of the pragmatic nature of the trials from which these data were collected, we do not have details of potentially important predictors, such as ejection fraction and induction medication doses. The accuracy of our model when calculated from passively collected electronic health record data or when simplified for use in clinical care is unknown. Therefore, use of our model as a bedside tool for prognostication should be discouraged until further validation studies are performed.

In summary, a model using preintubation risk factors can accurately predict cardiovascular collapse during tracheal intubation of critically ill adults. The model developed and validated in the present study may be used for analysis of heterogeneity of treatment effect or prognostic enrichment of future clinical trials.

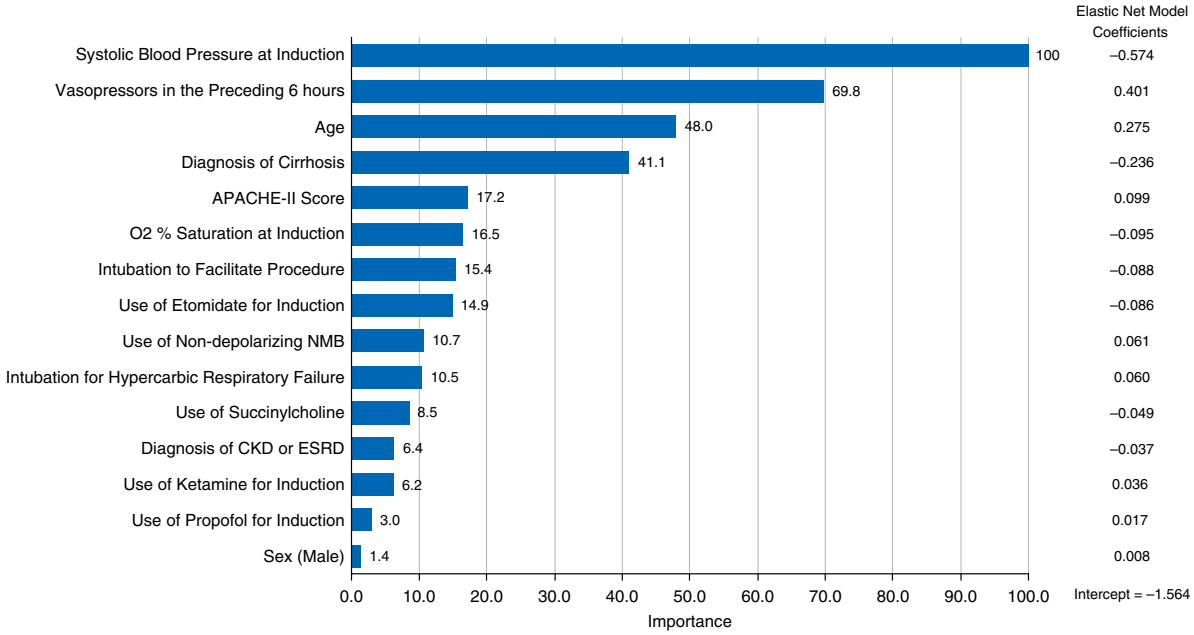

Figure 1. Importance of the predictor variables in the elastic net regression model, scaled to a maximum of 100 by using the absolute value of the variable coefficients and then scaling to a maximum value of 100. Coefficients (logarithmic odds scale) for the variables in the elastic net model are shown on the right. APACHE II = Acute Physiology and Chronic Health Evaluation II; CKD = chronic kidney disease; ESRD = end-stage renal disease; NMB = neuromuscular blockade.

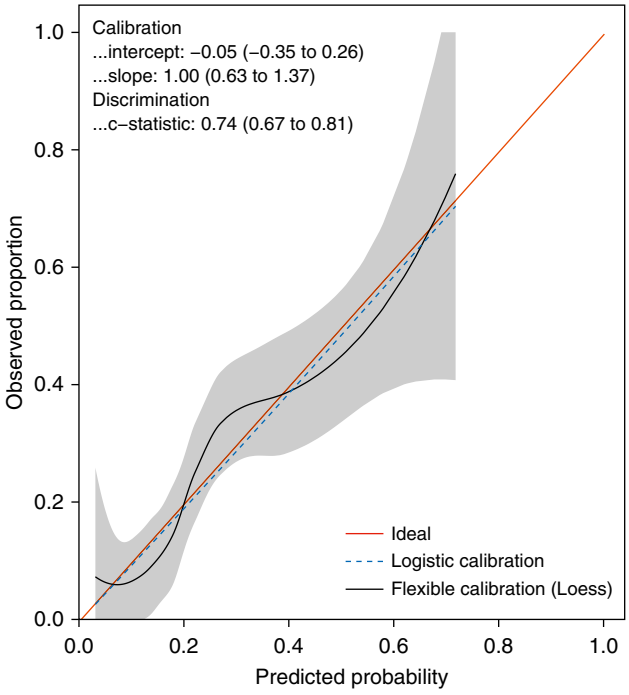

Figure 2. Model calibration in the Check-UP (Checklists and Upright Positioning in Endotracheal Intubation of Critically Ill Patients) trial (validation cohort), with a calibration intercept of −0.05 (95% confidence interval [CI], −0.35 to 0.26), a calibration slope of 0.99 (95% CI, 0.63 to 1.37), and an unreliability index $P = 0.96$.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Correlation between Ivacaftor-induced CFTR Activation in Airway Epithelial Cells and Improved Lung Function: A Proof-of-Concept Study

To the Editor:

Drugs have been developed that improve the primary cellular impairment in cystic fibrosis (CF) by increasing functional CFTR (CF transmembrane conductance regulator) protein in epithelial cells (1). Substantial biological and clinical effects were seen in clinical trials of ivacaftor, and more recently with a three-drug combination targeting the F508del mutation (2–4). The concentration of chloride in sweat (SwCl) is a central biomarker that is used to diagnose CF and to assess drug-induced improvement in CFTR function (5). Change in SwCl occurs within days of starting effective CFTR modulator drugs and is a useful predictor of clinical outcomes for groups based on a shared mutation, but has not performed as well for individual study participants (5). Many CF mutations are present in only a handful of people across the globe. This increases the need for alternative or complementary biomarkers that may predict individual clinical responses to drug therapy. For this purpose, cell-based assays of personalized *in vitro* CFTR function and response to drug exposure are currently being considered (6, 7).

We conducted a proof-of-concept study using an ongoing clinical research program in Dublin, Ireland, to collect primary airway epithelial cells (AECs) from participants treated with ivacaftor. This allowed us to test for a correlation between *in vitro* ivacaftor-induced CFTR activation and measures of both a change in SwCl and improved lung function (i.e., forced expiratory volume in 1 second (FEV_1)% predicted [FEV_1pp]) (8). We compared the strength of the correlation between improved lung function (i.e., clinical improvement) and *in vitro* ivacaftor-induced CFTR function versus the change in SwCl.

Methods

With institutional review board approval and informed consent from 12 adult individuals with either the G551D or R117H mutation, we collected nasal AECs by brushing the inferior nasal turbinate. Cells were placed in PneumaCult EX medium (Stemcell) supplemented with fluconazole (25 μg/ml) and antibiotics targeting CF pathogens (ceftazidime 100 μg/ml, tobramycin 100 μg/ml, and vancomycin 100 μg/ml), and transported warm between Dublin and Seattle, Washington, using vacuum-insulated Thermos containers with HotHands warm packs. Delays during shipping caused most of the cells to arrive ⩾3 days after they were collected rather than overnight. Upon arrival in Seattle, each brushing was seeded into a collagen-coated T25 flask and proliferated in submerged conditions until the cells reached 80% confluence (passage 0). One sample was insufficient and another experienced fungal overgrowth during transport. Six of the 10 remaining samples were expanded in submerged culture and passaged into collagen-coated, permeable, 12-mm-diameter Snapwell (Corning) Transwell inserts that were compatible with our Ussing chamber system (Physiologic Instruments, Inc.). They were then differentiated for 21 days at an