

Predicting physiologic response to changes in positive end-expiratory pressure in mechanically ventilated children: a computable phenotype and machine learning approach

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Research

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Abstract

Background

Positive end-expiratory pressure (PEEP) is often increased to improve ventilation efficiency and gas exchange during pediatric mechanical ventilation. Although it is clinically important to optimize PEEP in this population, there is a paucity of literature to guide the clinician at the bedside. Increasingly, time-series physiologic data are available for mechanically ventilated subjects in the intensive care unit. However, these data have not been adequately explored in the literature. Therefore, we sought to apply time-series computable phenotyping on time-series physiologic data and develop a model to predict PEEP response in mechanically ventilated children.

Methods

We conducted a retrospective analysis of continuous data in a academic hospital multidisciplinary intensive care unit. Patients were eligible for inclusion in the study if they received mechanically ventilation for > 25 hours and were < 18 years of age. Time-series data from the patient monitor and mechanical ventilator were abstracted 1-hour preceding and 1-hour following a PEEP change. PEEP increase (PEEP_{increase}), a responder was defined as anyone who exhibited an improved dead-space fraction (V_d/V_t); non-responders demonstrated a worsening V_d/V_t in the hour following the PEEP change. Features from continuous mechanical ventilation variables were extracted and used to train a support vector machine model in order to predict V_d/V_t response to changes in PEEP. The performance of the model was assessed by calculating the area under the receiver operator characteristic curve (AUROC) and computing measures of diagnostic accuracy.

Results

In all, 393 PEEP change cases were included in the analysis in 83 subjects. A total of 27 computable phenotypes were identified and incorporated into the model. The AUROC was 0.82 and 0.90 for classifying response to PEEP increases and decreases respectively. The overall diagnostic accuracy was 0.75 for PEEP increases and 0.84 for PEEP decreases.

Conclusions

The model classified responders to increases and decreases in PEEP with reasonable accuracy. The model performed better for those cases when PEEP was decreases. In the future, these methods may play an important role in optimizing care of the mechanically ventilated pediatric patients, especially if they can be tailored to individual institutions.

Background

Positive end-expiratory pressure (PEEP) is often increased to improve ventilation efficiency and gas exchange during pediatric mechanical ventilation. However, PEEP can ameliorate or exacerbate lung

injury.(1) Although it is clinically important to optimize PEEP in this population, there is a paucity of literature to guide clinicians at the bedside. The physiologic rationale for increasing PEEP is often to reduce physiologic dead-space fraction, improve oxygenation and lung mechanics as well as improve shunt fraction and ventilation/perfusion mismatch.(2–4) Ratio of dead-space to tidal volume ratio (V_d/V_t) has been associated with pediatric disease severity and success of ventilator weaning.(5, 6) Although the use of increased levels of PEEP has been shown to be safe in this population(7–10), widespread application within the pediatric intensive care unit has not been recommended and further work in this area is needed.(11, 12) Recently, we describe the baseline performance of bedside clinicians at selecting patients who will respond to increases or decreases in PEEP. (13) Of note, only 56% of PEEP increase cases demonstrated a subsequent improvement in oxygenation and 54% demonstrated an improvement in V_d/V_t .

Methods and techniques are needed to individualize care, reduce morbidity and duration of ventilation in the pediatric population.(11) Traditionally, gleaned robust representations of pediatric pathophysiology is especially difficult because the underlying causes of disease span body systems and physiologic processes, creating complex nonlinear relationships among observed measurements. This presents an important problem when designing experiments and transcribing medical data in a traditional sense. However, the increased connectivity of bedside medical devices as well as the availability of sophisticated time-series data analytics and machine learning offer an important opportunity in the modern intensive care unit.

Therefore, we sought to apply time-series computable phenotyping on time-series physiologic data and develop a model to predict PEEP response in mechanically ventilated children. A number of computable phenotypes are extracted from continuous physiologic data, important phenotypes are identified and used to train a machine learning model to identify those cases where a subject is likely to see an improvement in gas exchange following a manipulation of PEEP.

Methods

Subject selection

Subjects were eligible for inclusion in the study if they received mechanical ventilation for > 24 hours in the pediatric intensive care unit (PICU), age was less than 18 years, continuous mechanical ventilation data were recorded during that time period and they exhibited hypoxic respiratory failure defined as an oxygen saturation index ³5.(11)

Data collection

Mechanical ventilation was applied using the Servo-I (Getinge AB-Maquet, Gothenburg, Sweden) and connected to a physiologic monitor (IntelliVue MP90, Philips Healthcare, Andover, MA). The mechanical ventilator was interfaced to the monitor using the IntelliBridge medical device-interfacing module (model EC10, Philips Healthcare, Andover). Data was recorded at a frequency of 0.2Hz for the duration of stay in

the ICU. The variables included were peak inspiratory pressure (P_{peak}), positive end expiratory pressure (PEEP), total respiratory rate (RR), respiratory system compliance (C_{RS}), spontaneous respiratory rate ($\text{RR}_{\text{spontaneous}}$), fraction of inspired oxygen (FiO_2), expired minute ventilation (V_e), inspired minute ventilation (V_i), spontaneous minute ventilation ($V_{e\text{spontaneous}}$), mean airway pressure (P_{mean}), end-tidal CO_2 concentration (PetCO_2), volumetric CO_2 elimination (VCO_2), expired tidal volume (V_{te}), inspired tidal volume (V_{ti}), estimate of the pressure in the first 100ms of the breath (P_{100}), end-expiratory flow rate (V_{ee}), work of breathing of the ventilator (WOB_{vent}), barometric pressure (P_b), heart rate (HR), oxygen saturation (SpO_2) and dead-space fraction (V_d/V_t).

Demographic and outcome data were abstracted from the medical record for each subject and the diagnosis was recorded according to the International Classification of Diseases published by the World Health Organization (Revisions 9 and 10, Clinical Modification) and binned to either primary respiratory, surgical procedure, neurologic, sepsis or other.(14)

Data preprocessing

Because the procedures included in computable phenotype extraction often require the input data to be completely intact (no gaps in data), 1-dimensional linear interpolation was implemented for each variable. Further, the physiologic monitor and mechanical ventilator offer built-in preprocessing but signals can still be corrupted by noise and artifact.(15) Band-pass and low-pass filters were applied to filter out data that was not physiologically plausible according to established methods.(16) A Savitzky-Golay filter was applied to mechanical ventilation data in order to remove noise and artifact but preserve local data phenomenon.(17) Further, normalization of individual parameters is important in a pediatric population since signals are expected to change as the child grows. Data were normalized to either body weight (for respiratory parameters tidal volume, minute ventilation, carbon dioxide elimination, end-expiratory flow rate) and Z-scores were computed for heart rate and respiratory rate.(16, 18)

Case identification

For an individual subject, a case was defined as a 2-hour period, to include a 1-hour period preceding and 1-hour period following a change in PEEP. We have previously demonstrated that a period ~60 minutes is necessary to observe physiologic effects from modest changes in PEEP.(19) A quality function was built to ensure that only 'clean' cases were analyzed. A clean PEEP case was defined as one where no ventilator changes were made (other than PEEP and FiO_2); the PEEP change was sustained for > 1-hour. For cases where the PEEP was increased, a responder was defined as a case that exhibited any improvement in V_d/V_t ; $[V_d/V_{t_{\text{post}}} - V_d/V_{t_{\text{pre}}}] > 0$. For cases where PEEP was decreased, a responder was defined as a case where oxygenation was maintained; $[V_d/V_{t_{\text{post}}} - V_d/V_{t_{\text{pre}}}] \geq 0$.

Computable phenotype extraction

In most clinical investigations involving mechanical ventilation data, descriptive statistics are typically computed. However, since time-series data recorded at a relatively high frequency (compared to data transcribed in the electronic medical record), various representations of individual signals can be computed. Although thousands of methods exist in the literature, a set of 219 methods (including autocorrelation, auto-mutual information, stationarity, entropy, correlation dimension, linear and non-linear model fits, measures from the power spectrum and outlier quantification) provides a robust summary of the different behaviors of time series analysis.(20)

HCTSA has recently been applied in some areas of bioengineering, but applications on medical time-series data have not yet been studied.(21) We quantify a wide range of time series properties, computable phenotypes according to existing methods.(20)

Feature selection and model training

A small number of computable phenotypes were selected from the total set of phenotypes by implementing the least absolute shrinkage and selection operator according to established methods (LASSO).(22) A support vector machine (SVM) is a supervised machine learning algorithm that is applied to a wide variety of pattern recognition and classification problems and achieves good discriminative power in various healthcare data applications.(23-25) A separate model was trained for all cases where the PEEP was increased ($PEEP_{SVM}$) and where the PEEP was decreased ($PEEP^-_{SVM}$) since there are important differences in the disease acuity at times when PEEP would be increased or decreased. To protect against overfitting and to assess model performance a 5-fold cross validation was performed.

Statistical analyses

The D'Agostino and Pearson omnibus test was applied to test the normality of the data. Since the data were not normally distributed, continuous variables are presented as median (interquartile range). To assess model performance, the area under the receiver operator characteristic curve was calculated as well as the diagnostic accuracy, sensitivity, specificity, positive and negative predictive values and the positive and negative likelihood ratios. Data aggregation, cleaning and analyses were conducted using MATLAB (V9.1.0.441655, The Mathworks Inc., Natick, MA).

The protocol was approved by the Boston Children's Hospital Institutional Review Board and need for informed consent was waived.

Results

A total of 393 PEEP change cases were included in the analysis in 83 subjects. A general description of the population is shown in Table 1. An example of the time-series signals obtained during the present study are shown in Fig. 1.

Table 1
Description of the study population

Parameter	Median (IQR)*
Age (years)	2.1 (0.8–8.0)
Sex, n female (%)	36 (43)
Weight (kg)	11 (7.7–28.0)
Height (cm)	80 (66–116)
Vent duration (days)	5.8 (3.1–10.2)
ICU LOS (days)	12.0 (6.9–21.4)
Hospital LOS (days)	20.2 (6.4–49.2)
Primary diagnosis, n (%)	
Respiratory	23 (28)
Surgical	23 (28)
Sepsis	9 (11)
Neurologic	7 (8)
Other	21 (25)

Each of the 219 computable phenotype procedures were applied to each of the 22 variables included in the analysis. In all, 4818 computable phenotypes were quantified. Selection by LASSO identified a total of 27 computable phenotypes and were incorporated into the SVM model. The included clinical variables were the V_d/V_t , SpO_2 , HR, WOB_{vent} , P_{100} , VCO_2 , $PetCO_2$, P_{mean} , $VE_{spontaneous}$, VE, PEEP and P_{peak} and included information pertaining to the stationarity of the variable, linear and non-linear model goodness of fit for the predictor time period and objective outlier assessment.

The AUROC was 0.82 and 0.90 for classifying response to PEEP increases and decreases respectively. The overall diagnostic accuracy was 0.75 for PEEP increases and 0.84 for PEEP decreases. The performance of the models is depicted in Table 2.

Table 2
Model performance results

	PEEP↑	PEEP↓
Model type	SVM (Gaussian)	SVM (linear)
AUROC	0.82	0.90
Diagnostic accuracy	0.75	0.84
Sensitivity	0.75	0.81
Specificity	0.75	0.87
Positive Predictive Value	0.79	0.86
Negative Predictive Value	0.71	0.82
Positive Likelihood Ratio	3.05	6.22
Negative Likelihood Ratio	0.33	0.22

The receiver operator characteristic curves for the PEEP↑_{SVM} and PEEP↓_{SVM} models are depicted in Figs. 2A and 2B respectively.

Discussion

In mechanically ventilated children with hypoxic respiratory failure, the prediction models demonstrated diagnostic accuracy of 75% and 84% for PEEP increases and decreases respectively. The performance of the present models are superior to the empirical probability of improved condition following clinician directed alterations in PEEP.(13) The empirical probability of improved pulmonary condition defined as an improvement in dead-space fraction was 53.9% when increasing PEEP and 46.3% when decreasing PEEP.

The majority of pediatric investigations involving PEEP titration has been done in combination with a recruitment maneuver.(8, 26–28) In the pediatric literature, few studies have assessed the titration of PEEP without a recruitment maneuver. However, typical management of the child during mechanical ventilation includes the modest titration of PEEP (in increments ranging from 1–3 cmH₂O).(29) In a large multicenter, randomized controlled trial, a strategy included lung recruitment maneuvers and C_{RS} guided PEEP titration versus low PEEP demonstrated an increase in 28-day mortality.(30) In this study, the authors note the findings did not support routine lung recruitment combined with PEEP titration. Although this seems to suggest, at least in adult subjects with moderate to severe acute respiratory distress syndrome (ARDS) that PEEP titration may not be beneficial, it's not clear to what degree optimizing C_{RS} has on overall lung health. In the present study, we selected to use Vd/Vt as the target since has been associated with pediatric disease severity and success of ventilator weaning.(5, 6). Further, children have different pathophysiologic characteristics during lung injury relative to adults. Children have increased

chest wall compliance, they preserve the function of surfactant during injury have immune responses different than those of adult subjects.(31–33) For these reasons, it is difficult to make generalizations about pediatric mechanical ventilation based on adult data.

There are limitations to the present investigation that should also be considered. The nature of the study, being retrospective, precluded the strict control of how and when changes in PEEP were made. Factors pertaining to the subjects sedation regimen were not included. However, since spontaneous breathing parameters, including $RR_{\text{spontaneous}}$ and $Ve_{\text{spontaneous}}$, the end effects of any sedative or paralytic agents on the respiratory system are largely captured. Indeed, this approach may be superior to one that only includes dosing information for sedatives or paralytic agents. For example, subject A is receiving a high absolute dose of a sedative but manages to retain spontaneous breathing and subject B is receiving a modest absolute dose but is not breathing at all. One would expect that the fact that subject A is breathing spontaneously, this may be relevant when designing an algorithm to predict physiologic response; if only dosing information was captured, this information would be omitted. Subjects enrolled in the present study demonstrated a mix of demographics and underlying conditions; therefore, application of the findings to specific diseases may not be appropriate without further study. However, the cohort largely reflects a mix of conditions and severity of illness that is typically seen in large academic PICU environment.

Conclusions

The model classified responders to increases and decreases in PEEP with reasonable accuracy. The model performed better for those cases when PEEP was decreased. Of note, many computable phenotypes that were passed to the model describe characteristics of physiologic variables that are not readily identified at the bedside. In the future, these methods may play an important role in optimizing care of the mechanically ventilated pediatric patients.

Declarations

Ethics approval and consent to participate

The Boston Children's Hospital Institutional Review Board approved the present study and need for informed consent was waived since the analysis utilized retrospectively collected data.

Consent for publication

No individual participant data is reported that would require consent to publish from the participant.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no competing interests to disclose.

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Author contributions

CDS, AG and JHA were responsible for the conception and study design. CDS was responsible for data collection and analysis. All authors were responsible for interpreting the study results. CDS was responsible for drafting the manuscript. All authors read and approved the final manuscript.

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References

1. Kallet RH. Should PEEP Titration Be Based on Chest Mechanics in Patients With ARDS? *Respir Care*. 2016;61(6):876-90.
2. von Ungern-Sternberg BS, Regli A, Schibler A, Hammer J, Frei FJ, Erb TO. The impact of positive end-expiratory pressure on functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen. *Anesth Analg*. 2007;104(6):1364-8, table of contents.
3. Rimensberger PC, Pache JC, McKerlie C, Frndova H, Cox PN. Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both

- conventional mechanical ventilation and high-frequency oscillation. *Intensive Care Med.* 2000;26(6):745-55.
4. Papadakos PJ, Lachmann B. The open lung concept of mechanical ventilation: the role of recruitment and stabilization. *Crit Care Clin.* 2007;23(2):241-50, ix-x.
 5. Almeida-Junior AA, da Silva MT, Almeida CC, Ribeiro JD. Relationship between physiologic deadspace/tidal volume ratio and gas exchange in infants with acute bronchiolitis on invasive mechanical ventilation. *Pediatr Crit Care Med.* 2007;8(4):372-7.
 6. Hubble CL, Gentile MA, Tripp DS, Craig DM, Meliones JN, Cheifetz IM. Dead-space to tidal volume ratio predicts successful extubation in infants and children. *Crit Care Med.* 2000;28(6):2034-40.
 7. Duff JP, Rosychuk RJ, Joffe AR. The safety and efficacy of sustained inflations as a lung recruitment maneuver in pediatric intensive care unit patients. *Intensive Care Med.* 2007;33(10):1778-86.
 8. Kheir JN, Walsh BK, Smallwood CD, Rettig JS, Thompson JE, Gomez-Laberge C, et al. Comparison of 2 lung recruitment strategies in children with acute lung injury. *Respir Care.* 2013;58(8):1280-90.
 9. Cruces P, Donoso A, Valenzuela J, Diaz F. Respiratory and hemodynamic effects of a stepwise lung recruitment maneuver in pediatric ARDS: a feasibility study. *Pediatr Pulmonol.* 2013;48(11):1135-43.
 10. Boriosi JP, Sapru A, Hanson JH, Asselin J, Gildengorin G, Newman V, et al. Efficacy and safety of lung recruitment in pediatric patients with acute lung injury. *Pediatr Crit Care Med.* 2011;12(4):431-6.
 11. Pediatric Acute Lung Injury Consensus Conference G. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015;16(5):428-39.
 12. Jauncey-Cooke J, East CE, Bogossian F. Paediatric lung recruitment: a review of the clinical evidence. *Paediatr Respir Rev.* 2015;16(2):127-32.
 13. Smallwood CD, Walsh BK, Arnold JH, Gouldstone A. Empirical Probability of Positive Response to PEEP Changes and Mechanical Ventilation Factors Associated With Improved Oxygenation During Pediatric Ventilation. *Respir Care.* 2019;64(10):1193-8.
 14. Classification TCoC. International Classification of Diseases - 9 - CM Centers for Disease Control and Prevention; 1979 [Available from: https://wonder.cdc.gov/wonder/sci_data/codes/icd9/type_txt/icd9cm.asp].
 15. Clifford GD, Behar J, Li Q, Rezek I. Signal quality indices and data fusion for determining clinical acceptability of electrocardiograms. *Physiol Meas.* 2012;33(9):1419-33.
 16. Bonafide CP, Brady PW, Keren R, Conway PH, Marsolo K, Daymont C. Development of heart and respiratory rate percentile curves for hospitalized children. *Pediatrics.* 2013;131(4):e1150-7.
 17. Savitzky A, Golay MJE. Smoothing and Differentiation of Data by Simplified Least Squares Procedures. *Analytical Chemistry.* 1964;36(8):1627-39.
 18. Chubb H, Simpson JM. The use of Z-scores in paediatric cardiology. *Ann Pediatr Cardiol.* 2012;5(2):179-84.

19. Smallwood CD, Walsh BK, Arnold JH, Gouldstone A. Equilibration time required for respiratory system compliance and oxygenation response following changes in positive end-expiratory pressure in mechanically ventilated children. *Crit Care Med*. 2018;(in press).
20. Fulcher BD, Little MA, Jones NS. Highly comparative time-series analysis: the empirical structure of time series and their methods. *J R Soc Interface*. 2013;10(83):20130048.
21. Chen CR, Shu WY, Chang CW, Hsu IC. Identification of under-detected periodicity in time-series microarray data by using empirical mode decomposition. *PLoS One*. 2014;9(11):e111719.
22. Tibshirani R. Regression shrinkage selection via the LASSO 2011. 273-82 p.
23. Son YJ, Kim HG, Kim EH, Choi S, Lee SK. Application of support vector machine for prediction of medication adherence in heart failure patients. *Healthc Inform Res*. 2010;16(4):253-9.
24. Yu W, Liu T, Valdez R, Gwinn M, Khoury MJ. Application of support vector machine modeling for prediction of common diseases: the case of diabetes and pre-diabetes. *BMC Med Inform Decis Mak*. 2010;10:16.
25. Kennedy CE, Aoki N, Mariscalco M, Turley JP. Using Time Series Analysis to Predict Cardiac Arrest in a PICU. *Pediatr Crit Care Med*. 2015;16(9):e332-9.
26. Hanson A, Gothberg S, Nilsson K, Hedenstierna G. Lung aeration during ventilation after recruitment guided by tidal elimination of carbon dioxide and dynamic compliance was better than after end-tidal carbon dioxide targeted ventilation: a computed tomography study in surfactant-depleted piglets. *Pediatr Crit Care Med*. 2011;12(6):e362-8.
27. Hanson A, Gothberg S, Nilsson K, Larsson LE, Hedenstierna G. VTCO₂ and dynamic compliance-guided lung recruitment in surfactant-depleted piglets: a computed tomography study. *Pediatr Crit Care Med*. 2009;10(6):687-92.
28. Wolf GK, Gomez-Laberge C, Rettig JS, Vargas SO, Smallwood CD, Prabhu SP, et al. Mechanical ventilation guided by electrical impedance tomography in experimental acute lung injury. *Crit Care Med*. 2013;41(5):1296-304.
29. Khemani RG, Parvathaneni K, Yehya N, Bhalla AK, Thomas NJ, Newth CJL. PEEP Lower Than the ARDS Network Protocol is Associated with Higher Pediatric ARDS Mortality. *Am J Respir Crit Care Med*. 2018.
30. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial I, Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA*. 2017;318(14):1335-45.
31. Papastamelos C, Panitch HB, England SE, Allen JL. Developmental changes in chest wall compliance in infancy and early childhood. *J Appl Physiol* (1985). 1995;78(1):179-84.
32. LeVine AM, Lotze A, Stanley S, Stroud C, O'Donnell R, Whitsett J, et al. Surfactant content in children with inflammatory lung disease. *Crit Care Med*. 1996;24(6):1062-7.

33. Smith LS, Zimmerman JJ, Martin TR. Mechanisms of acute respiratory distress syndrome in children and adults: a review and suggestions for future research. *Pediatr Crit Care Med.* 2013;14(6):631-43.

Figures

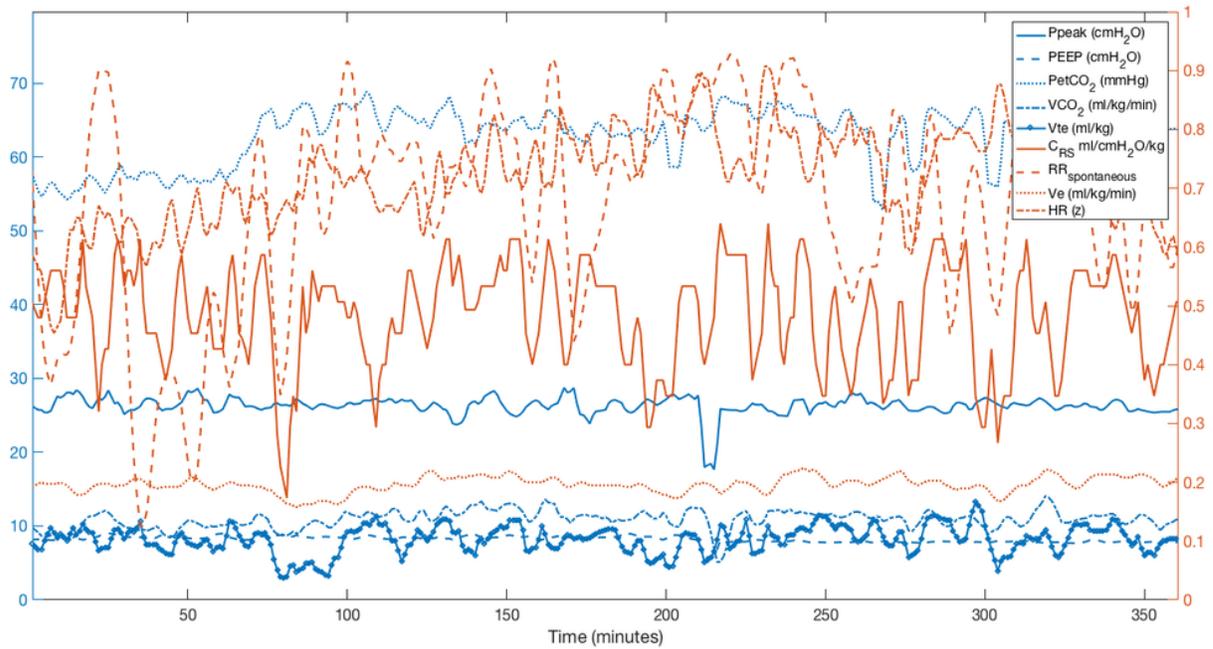


Figure 1

Time-series data from a single patient. Feature in blue are plotted on the left y-axis and feature in red are plotted on the right y-axis.

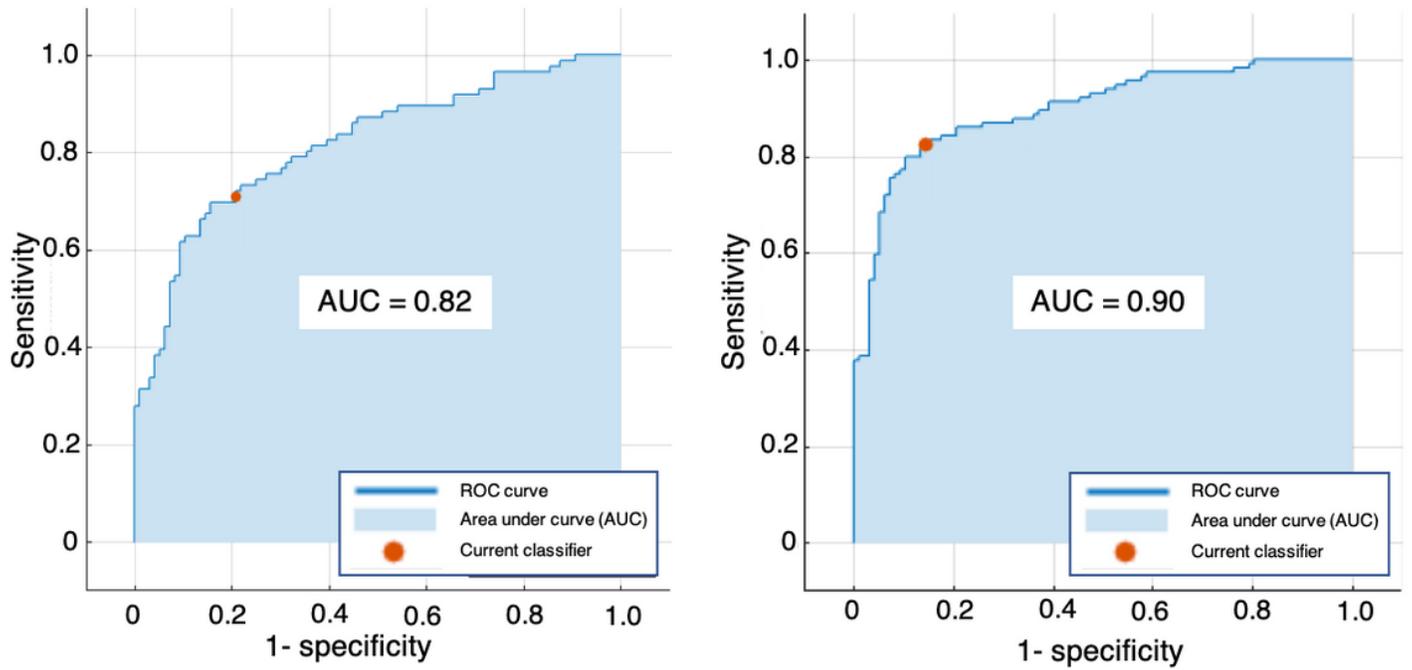


Figure 2

A: Receiver operator characteristic curve for the PEEP increase model. B: Receiver operator characteristic curve for the PEEP decrease model.

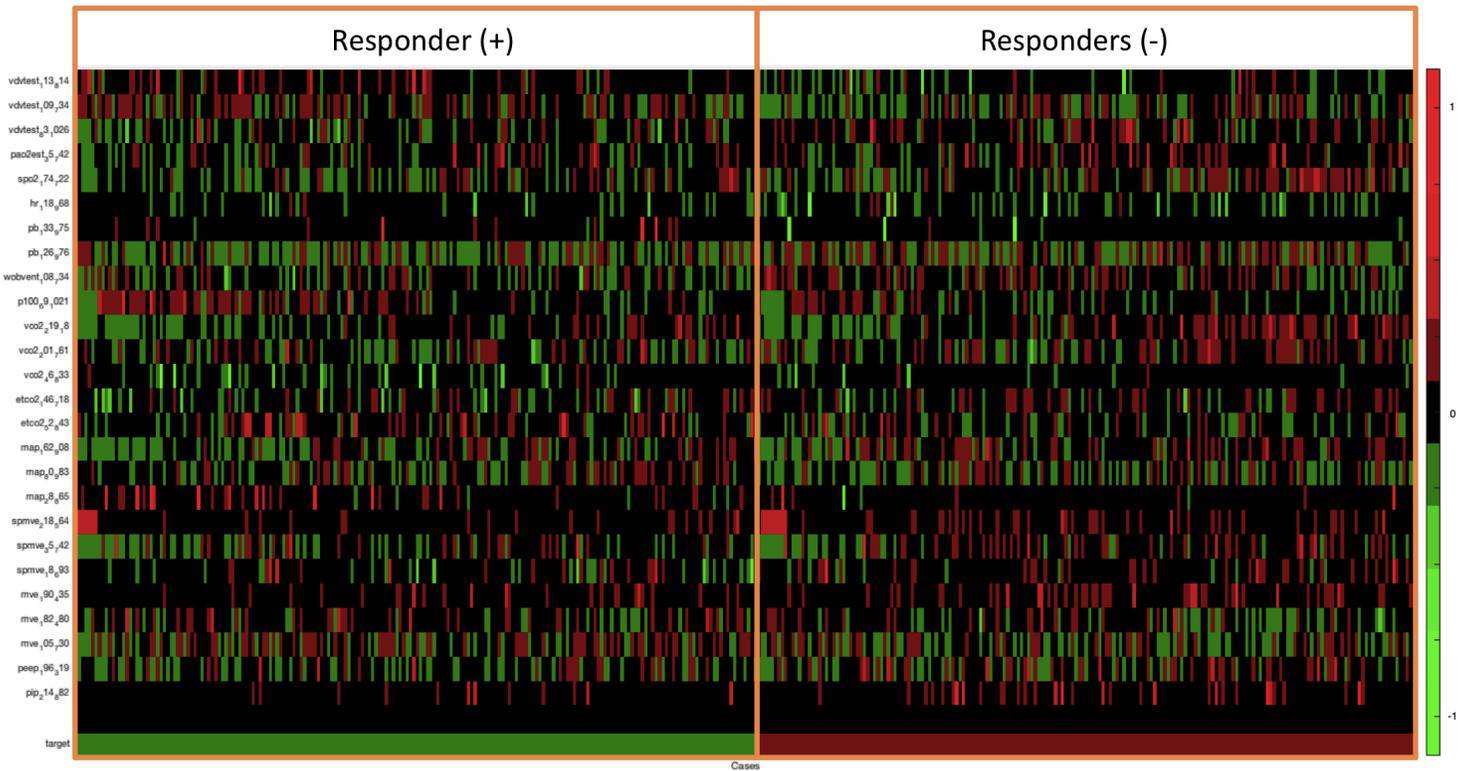


Figure 3

A visual summary of the computable phenotypes including in the model for increases in positive end expiratory pressure and the corresponding response classification. Each row corresponds to a phenotype and each column corresponds to an individual subject. The cases were organized such that responders are on the left (Responder +) and non-responders are on the right (Responder -). The results were standardized to zero mean. Values above the mean are depicted in red and values below the mean are depicted in green.