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In Silico Trial for Preclinical Evaluation of an Automated Weaning Protocol

C. Hennigs[1,2*], F. Bilda[1,2], G. Männel[2], and P. Rostalski[1,2]

[1] *Institute for Electrical Engineering in Medicine, Universität zu Lübeck, Lübeck, Germany*
[2] *Fraunhofer Research Institution for Individualized Medical Engineering, Lübeck, GermanyDa*
[*] *Corresponding author, email: carlotta.hennigs@uni-luebeck.de*

Abstract: In silico clinical trials (ISCTs) may reduce risks of automated ventilation by evaluating performance across physiologic variability with traceable model credibility. We present a case study using a patient–device model (PDM) to assess an automated weaning function in ICU patients. The workflow defines the question of interest, context of use, cohort/scenario generation, sampling, execution, and analysis. A virtual ICU cohort captures variability in demographics and pathophysiology (ARDS, COPD, postoperative, neuromuscular, cardiopulmonary) using literature-based parameters. Nine scenarios test robustness, including elastance/resistance steps, drive shifts, shunt/dead-space increases, and sedation taper. Primary endpoints are time in target for tidal volume (V_T), respiratory rate (RR), and end-tidal CO_2 ($etCO_2$), excursion durations, and overshoot. Respiratory rate and $etCO_2$ remained ≥80% in target, while V_T only remained in target range about 50 % due to narrow protective bounds. This compact ISCT provides a credibility-aware framework for evaluation of automated protocols, shown here as an example for weaning.

I. Introduction

Automation in mechanical ventilation is becoming more and more relevant in an aging society. Yet evaluation of such algorithms is limited by costs, complexity, and risk constraints. In silico clinical trials (ISCTs) offer structured, risk-informed evidence complementing bench and in vivo testing. The main purpose of this publication is to illustrate the execution of a simplified ISCT for mechanical ventilation according to ASME V&V 40 [1], serving as a blueprint for other ISCTs. The case study evaluates an automated weaning function (AWF) that adjusts pressure support every 120 s during CPAP based on respiratory rate, tidal volume, and end-tidal CO_2 ($etCO_2$) to maintain lung-protective ventilation and introduce weaning from the ventilator, following a description of the *Dräger SmartCare/PS* protocol as described in [2].

In this work, an ISCT workflow is defined, a virtual ICU cohort is constructed using literature-based parameters, targeted stress scenarios are designed, and relevant performance metrics are reported. This approach generates concise, credibility-aware evidence to support iterative development, design refinement, and preclinical evaluation of ventilator automation.

II. Methods

II.I. Workflow of in silico trial

The ISCT workflow is shown in Figure 1 and comprises several sequential steps, based on the ASME V&V 40 [1]. First, the question of interest (?oI) and context of use (COU) are defined to set the scope of the study. Next, the required model components and quantities of interest (QoIs) are specified and implemented. The virtual patient cohort and clinical scenarios are then defined accordingly. Once established, simulations are executed and results analyzed.

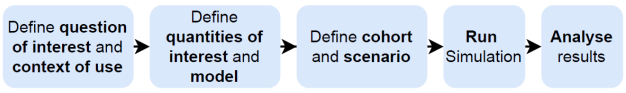

Figure 1: Workflow for in silico clinical trials (ISCT).

II.II. Definitions and set up of ISCT

Question of Interest (?oI): Can the AWF maintain tidal volume (V_T) and respiratory rate (RR) within targets while keeping end-tidal CO_2 within an acceptable range when operated in intended use?

Context of Use (COU): Preclinical evaluation of an automated weaning function for adult ICU patients during assisted ventilation. The ISCT is not intended to inform patient-specific clinical decisions.

Quantities of Interest (QoI): Tidal volume (V_T), respiratory rate (RR), and end-tidal CO_2 ($etCO_2$).

Patient-Device model: A coupled patient–device model (PDM) was used, comprising lung mechanics with nonlinear elastance and resistance to represent ARDS and COPD phenotypes. Gas exchange is simulated on a breath-resolved basis, including shunt and dead-space components [3]. The respiratory controller includes chemoreflex and mechanoreflex pathways to capture patient–ventilator interaction, following the framework described in [4]. As device, ventilator logic with pressure controller and the AWF is implemented.

Cohort and scenario generation: A virtual ICU cohort of $N = 50$ patients is generated. Parameter ranges representative of an adult ICU population are provided in Table 1, and disease-specific perturbations and scenario variations are summarized in Table 2. Model parameterization follows the work of Merrath et al. [5].

Table 1: Virtual ICU patient population: Age, sex, height and BMI (body mass index) [6].

Age [y]	Median: 82
Sex	64% male / 36% female
Height [m]	male: 1.76 ± 0.07, female: 1.64 ± 0.07
BMI [kg/m²]	<20 (5%), 20–25 (40%), 25–30 (35%), 30–39 (15%), ≥40 (5%)

Table 2: Disease distribution of virtual patient cohort and model parameter perturbations [7]. f_s: shunt fraction, f_{VD}: pulmonary dead space fraction, R_{exp}: expiratory airway resistance, C_L: lung compliance, Q: Cardiac output, ARDS: Acute respiratory distress syndrome, COPD: Chronic obstructive pulmonary disease, RASS: Richmond agitation-sedation scale.

ARDS	30%	$f_s = 0.29$, $f_{VD} = 0.3$, decreased C_L
COPD	30%	$f_s = 0.12$, $f_{VD} = 0.12$, increased R_{exp}
Postoperative	25%	RASS = -3
Neuromuscular	10%	Resp. failure = 40%
Lung edema	5%	f_s=0.25, decrease in Q

Scenarios and sampling: For the purpose of this article, nine scenarios are implemented to evaluate robustness across relevant physiological and clinical conditions. These include a baseline condition, step changes in elastance and resistance, alterations in respiratory drive (representing sedation or respiratory failure), increases in shunt and (pulmonary) dead space, and a sedation-taper scenario mimicking weaning. Representative parameter ranges are explored using Latin hypercube sampling. Each simulation runs for 2000 s, with perturbations introduced at 800 s and weaning-related adjustments staggered over time.

III. Results and discussion

The pass criterion for Time in Target (TiT) is defined as V_T = 4–8 mL·kg^{-1} IBW (ideal body weight), RR = 10–30 min^{-1}, and $etCO_2$ = 25–55 mmHg ≥80%, excursion duration outside targets ≤120 s, and maximum overshoot ≤30%. Means ± SD and medians are reported per scenario, along with a pass/fail overview (Figure 2).

Across most scenarios, RR and $etCO_2$ achieve ≥80% TiT, while V_T TiT is around 50 % for all scenarios. Excursion durations are shortest for RR, reflecting rapid controller adaptation, and longest for $etCO_2$, reflecting slower gas-exchange kinetics and the 120 s update cadence. V_T excursions are sporadic but could be prolonged in some patient–scenario combinations (e.g., high resistance or sudden elastance/drive changes), with low median overshoot, indicating operation near target boundaries rather than sustained over-assistance.

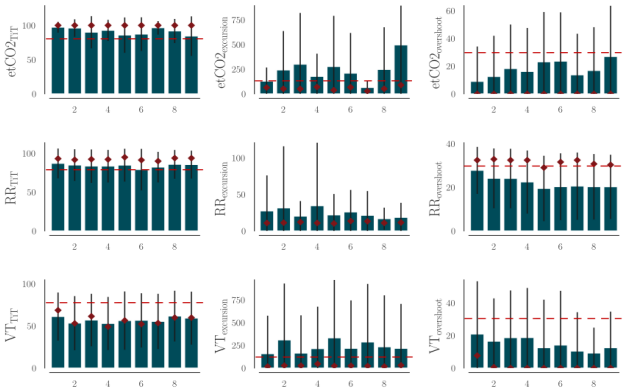

Figure 2: Mean (blue bars ± SD) and median (red diamonds) of end-tidal CO_2 ($etCO_2$), respiratory rate (RR), and tidal volume (V_T) across all scenarios. TiT: Time in Target [%], excursion [s], overshoot [%].

This brief description of an ISCT illustrates a credibility aware, preclinical evaluation of an AWF using a physiologically grounded PDM. Key signals (RR, $etCO_2$) remained in target across variability. V_T control was the most demanding due to tighter protective bounds and disease driven mechanics (COPD flow limitation, ARDS elastance heterogeneity).

IV. Conclusion

A concise ISCT using a physiologically based patient–device model provides actionable evidence for an automated weaning function. RR and $etCO_2$ targets are largely maintained, while V_T remained most challenging under pathophysiologic variability. Future analyses could investigate the influence of patient-specific parameters. This compact workflow supports iterative design and preclinical evaluation, complementing bench tests and in vivo testing.

Author's Statement

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