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Anemia at extubation: association with reintubation, practices over time and impact on respiratory effort

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ABSTRACT

Background: Anemia is common in critically ill patients and may contribute to extubation failure by impairing oxygen delivery and increasing respiratory effort. However, practices are understudied and the impact of anemia on extubation remains poorly understood.
We aimed to assess the association between low hemoglobin and extubation outcomes, clinical practices regarding hemoglobin levels at extubation, and the impact on respiratory effort.

Methods: We first conducted a retrospective analysis of prospectively collected data from consecutive adults extubated after ≥24 hours of invasive mechanical ventilation in a tertiary intensive care unit between 2016 and 2024. Patients were categorized according to hemoglobin at extubation <9 or ≥9 g/dL, which defined the primary exposure. The primary outcome was 7-day reintubation, assessed using the Aalen–Johansen estimator and Fine–Gray models, with death as a competing event. Secondly, the temporal trend in hemoglobin level at extubation was assessed using restricted cubic splines.
Thirdly, we performed a post hoc analysis of two physiological randomized controlled trials evaluating inspiratory effort using esophageal pressure measurements before and after extubation. The association between pre-extubation hemoglobin and changes in inspiratory effort after extubation was assessed using adjusted linear regression.

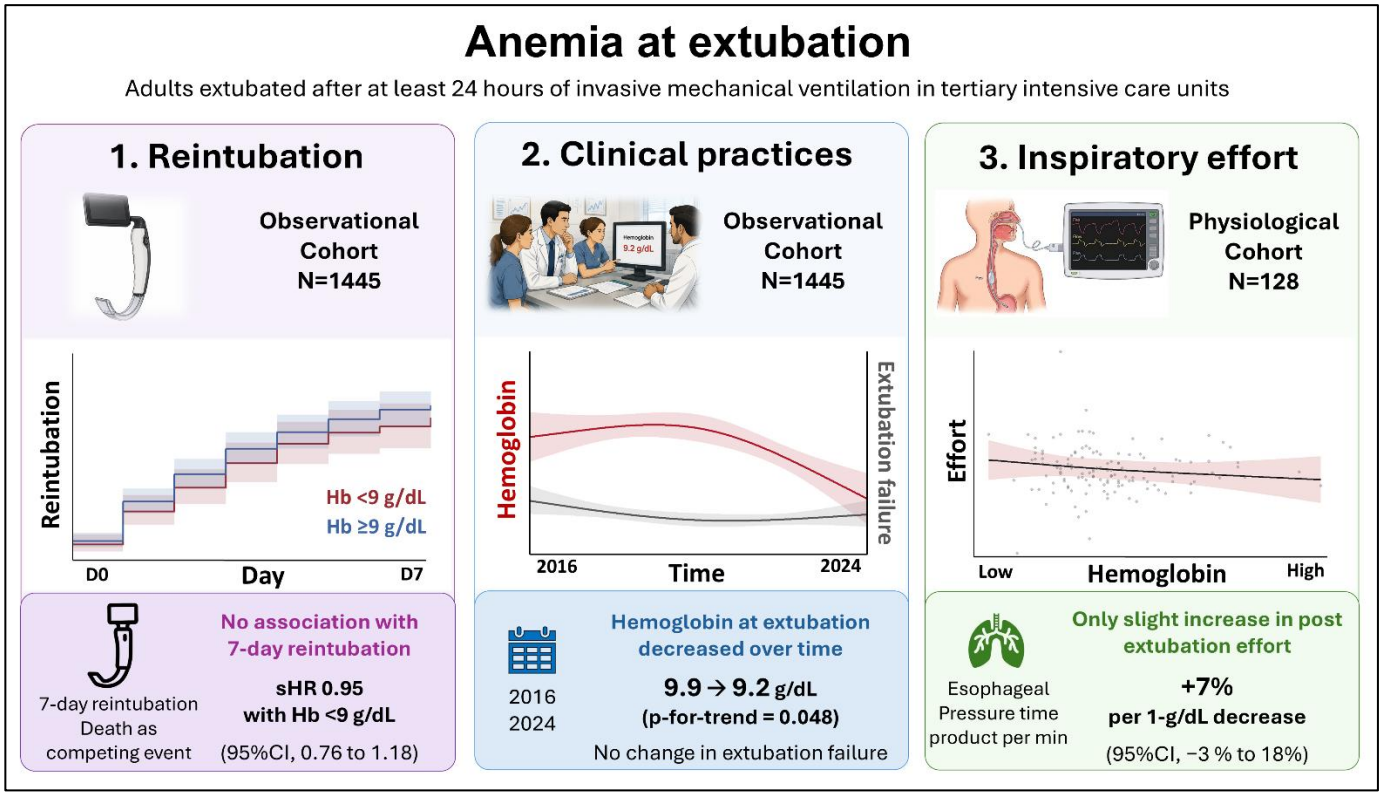
Results:
A total of 1445 patients in the observational cohort and 128 patients in the physiological cohort were included. The 7-day cumulative incidence of reintubation was 21.6% (95%CI, 18.2–25.1%) in patients with hemoglobin <9 g/dL and 23.5% (95%CI, 20.8–26.3%) in those with hemoglobin ≥9 g/dL. After adjustment, hemoglobin <9 g/dL was not associated with 7-day reintubation (sHR 0.95, 95%CI 0.76–1.18; p=0.640). The median hemoglobin level at extubation decreased over time, from 9.9 g/dL in 2016 to 9.2 g/dL in 2024 (p-for-trend=0.048). Inspiratory effort increased in overall physiological cohort population by 59% across extubation, and lower hemoglobin was associated with a slightly greater increase, although not statistically significant (pressure-time-product per minute +7.4% per 1-g/dL hemoglobin decrease; 95%CI, −3.3% to 18.2%; p=0.174).

Conclusions:
Low hemoglobin was not independently associated with extubation failure. Hemoglobin levels at extubation decreased over time, suggesting more liberal extubation practices. Lower hemoglobin showed only a modest trend toward increased post-extubation inspiratory effort.

Trial registration: ClinicalTrials.gov NCT01616901 (2012, June 4th), and NCT04222569 (2019, December 9th)

Keywords: critical care, anemia, mechanical ventilation, extubation

GRAPHICAL ABSTRACT



BACKGROUND

Anemia, defined by the World Health Organization (WHO) as a hemoglobin level <12 g/dL in non-pregnant women and <13 g/dL in men[1], is highly prevalent in critically ill patients, affecting approximately 60% at intensive care unit (ICU) admission[2,3] and 80% at discharge.[3,4] Hemoglobin is a major determinant of arterial oxygen content and oxygen delivery[5] and its reduction may become particularly critical during the transition to spontaneous breathing, which increases respiratory effort and the oxygen cost of breathing.[6–9] Beyond this potential mismatch between oxygen demand and delivery, anemia itself may further increase respiratory workload as a compensatory response[10], although direct evidence is lacking. Among mechanically ventilated ICU patients, whether this may affect extubation outcomes remains unclear.

Previous observational studies have suggested an association between lower hemoglobin levels and extubation failure, with reported thresholds ranging from 7.5 to 10 g/dL.[11–13] A meta-analysis further suggested lower hemoglobin at extubation as associated with extubation failure without threshold identified.[14] However, although not specifically focused on extubation, randomized controlled trials (RCTs) comparing different hemoglobin thresholds found no difference in the duration of mechanical ventilation between conservative lower and liberal higher hemoglobin targets.[15,16] Earlier weaning guidelines referenced hemoglobin targets of ≥8–10 g/dL,[17] but these thresholds progressively disappeared due to limited evidence.[18] More recent guidelines only address prolonged mechanical ventilation, conditionally favoring a restrictive threshold of 7 g/dL over 9 g/dL based on low-certainty evidence.[19]

Given the remaining physiological and clinical uncertainty surrounding anemia at extubation, along with the shift from specific hemoglobin targets to the absence of clear recommendations, we aimed to assess the association between anemia and extubation outcomes, clinical practices regarding hemoglobin levels at extubation and the impact on post-extubation inspiratory effort.

METHODS

Study design

We first conducted a retrospective analysis of prospectively collected data from consecutive adult patients mechanically ventilated in a tertiary 20-bed ICU between 2016 and 2024. This observational study was approved by the Montpellier University Institutional Review Board (2019_IRB-MTP_05–25), conducted in accordance with the Declaration of Helsinki, and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

Second, we performed a post hoc analysis of two prospective randomized crossover physiological trials[6,9,21] evaluating inspiratory effort before and after extubation using esophageal pressure measurements. The first trial was approved by the Comité de Protection des Personnes Sud Méditerranée III (2012-A00294-39) and registered at ClinicalTrials.gov (NCT01616901; June 4, 2012).[21] The second trial was conducted in 3 centers, approved by the Comité de Protection des Personnes TOURS–Région Centre–Ouest 1 (2019-A01063-54) and registered at ClinicalTrials.gov (NCT04222569; December 9, 2019).[6,9] Written informed consent was obtained from all patients or, when applicable, their surrogate, according to the procedures of the original trials.

Population

The observational cohort included consecutive adult patients who underwent extubation after at least 24 hours of invasive mechanical ventilation. Analyses were conducted at the patient level. In cases of multiple ICU stays or ventilation periods, only the first invasive mechanical ventilation period lasting at least 24 hours was considered. Patients who underwent tracheostomy before extubation or received palliative care were not eligible. High risk of extubation failure was defined as age >65 years or underlying chronic cardiac or respiratory disease.[22] Patients were categorized into two groups according to their hemoglobin level at extubation: <9 g/dL and ≥9 g/dL.[16,17,19]

The physiological cohort included consecutive adult patients from the two randomized crossover trials who had received invasive mechanical ventilation for at least 24 hours and were considered ready for extubation by the clinician in charge. Eligibility criteria and trial-specific exclusion criteria have been previously reported.[6,9,21] For the present

analysis, patients with available pre-extubation hemoglobin and inspiratory effort measurements before and after extubation were included.

Data collection

In the observational cohort, data were prospectively collected by the research team throughout the ICU stay using a standardized approach. Data sources included automatically recorded bedside monitoring and ventilator data, laboratory results, nursing and medical electronic records, and, when needed, clarification with the bedside clinical team. These prospectively collected data were subsequently extracted from the ICU research database for the present retrospective analysis. Collected variables included demographics, anthropometrics, comorbidities, admission characteristics, severity scores, mechanical ventilation characteristics, fluid balance, and clinical and biological variables throughout the ICU stay. Data specifically related to extubation included respiratory and ventilatory parameters, hemoglobin level, red blood cell (RBC) transfusion during the 24 hours preceding extubation, and post-extubation outcomes.

In the physiological cohort, individual patient data were obtained from the two randomized crossover trials.[6,9,21] Inspiratory effort was assessed using esophageal pressure measurements at baseline under mechanical ventilation and 20 minutes after extubation, following a one-hour resting period under baseline ventilatory settings after spontaneous breathing trial. Measurements after extubation were done without assistance, with only oxygen standard therapy at a flow rate to achieve a SpO2 similar to that prior to extubation.

Exposure and outcomes

The primary exposure was hemoglobin level at extubation, defined as the last available measurement within 24 hours before extubation. The primary outcome for the reintubation analysis was reintubation within 7 days after extubation, with death before reintubation considered as a competing event. Secondary outcomes included reintubation within 48 and 72 hours after extubation, with death considered as a competing event, 28-day mortality and ventilator-free days (VFDs) at day 28. VFDs were defined as the number of days alive and free from invasive mechanical ventilation within 28 days after extubation, with patients who died assigned zero VFDs. A composite

outcome of extubation failure at day 7, defined as reintubation or death within 7 days after extubation, was also used in secondary analyses.

In the physiological cohort, arterial blood gas measurements were protocolized, and hemoglobin level was obtained from the arterial blood gas sample collected at the end of the spontaneous breathing trial, immediately before extubation. The outcome of interest was the change in inspiratory effort from baseline under mechanical ventilation to after extubation and its association with hemoglobin level. Pressure–time product per minute (PTPes/min) was the primary outcome. Esophageal pressure swing (SwingPes) and PTPes quantified the magnitude and time-integrated magnitude of inspiratory effort per breath, respectively, while SwingPes/min and PTPes/min quantified the corresponding inspiratory effort per minute.

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median [interquartile range], as appropriate, and categorical variables as number (percentage). Comparisons between hemoglobin groups were performed using the Student's t-test or Wilcoxon rank-sum test for continuous variables, as appropriate, and the chi-square test for categorical variables.

Assuming a 7-day reintubation rate of up to 18% based on our previous data[23] in patients with hemoglobin ≥9 g/dL and an anticipated rate of 25% in patients with hemoglobin <9 g/dL based on the reported association between anemia and reintubation,[11–14] a minimum sample size of approximately 1,076 patients would be required to achieve 80% power with a two-sided type I error of 5%. For the physiological analysis, based on the reported effect of hemoglobin on inspiratory effort[10] and previously reported PTPes values before and after extubation,[6] we anticipated a difference of approximately 20 $cmH_2O \cdot s/min$ in PTPes/min change per 1-g/dL difference in hemoglobin. A sample size of 120 patients would provide 80% power to detect this association with a two-sided type I error of 5%.

The cumulative incidence of reintubation by day 7 was estimated using the Aalen–Johansen estimator, with death before reintubation considered as a competing event.[24]

The association between hemoglobin level at extubation and reintubation at day 7 was assessed using Fine–Gray competing-risk regression. Adjusted absolute risks and risk differences at day 7 were obtained by marginal standardization (g-computation) from the Fine–Gray model, with 95% confidence intervals estimated using 1,000 non-parametric bootstrap resamples. Reintubation at 48 and 72 hours was analyzed using the same competing-risk approach. Day-28 mortality was assessed using Cox proportional hazards regression, and ventilator-free days at day 28 using proportional-odds ordinal logistic regression.[25] Covariates for the primary adjusted models were selected a priori based on clinical knowledge and a directed acyclic graph (**Figure S1**).[26] Adjusted models included age, body mass index, surgical admission, chronic respiratory disease, chronic cardiac disease, SAPS II at admission, coma at admission, duration of mechanical ventilation before extubation, fluid balance during the 24 hours before extubation, and SOFA score at extubation. Results are reported as subdistribution hazard ratios (sHRs), hazard ratios (HRs), and odds ratios (ORs), respectively, with 95% confidence intervals. Hemoglobin was primarily analyzed using a threshold of 9 g/dL and additionally as a continuous variable, with potential nonlinear associations explored using restricted cubic splines with three knots.

Sensitivity analyses assessed the robustness of the findings to alternative model specifications, population restrictions, and hemoglobin thresholds. An expanded adjustment model additionally included variables with a standardized mean difference >0.10 between hemoglobin groups, including SOFA score at admission, chronic kidney disease, current alcohol use disorder, acute kidney injury, postoperative liver transplantation, and massive hemorrhage. SOFA score at extubation was the only adjustment variable with missing data (approximately 5%) and was imputed using the cohort median in the primary analyses. Sensitivity analyses included a complete-case analysis and a model excluding SOFA score at extubation. Additional subgroup analyses were performed.

Temporal trends from 2016 to 2024 were modeled using the exact date of extubation as a continuous time variable and restricted cubic splines (RCS) with three knots positioned at Harrell's recommended percentiles. Trends in annual mean hemoglobin levels and mean RBC units administered among transfused patients were assessed using the Mann–

Kendall test, with the magnitude of change estimated using Sen's slope. Trends in the proportions of patients with extubation failure and receiving RBC transfusion were assessed using the Cochran–Armitage trend test.[27]

For the physiological analysis, associations between hemoglobin level and changes in inspiratory effort from before to after extubation were assessed using multivariable linear regression adjusted for clinically relevant determinants of inspiratory effort, including the type of critical illness, baseline pressure support (PSV), baseline positive end-expiratory pressure (PEEP), baseline (pre-SBT) maximal inspiratory pressure (MIP) and fluid balance before extubation. Potential nonlinear associations were explored using restricted cubic splines with three knots. As a sensitivity analysis, robust linear regression was performed to assess the influence of outliers.[28] Additionally, changes in inspiratory effort were compared across hemoglobin categories using Wilcoxon rank-sum tests.

All tests were two-sided, and a p-value <0.05 was considered statistically significant. Analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population

Between January 2016 and December 2024, 1,445 patients were included (**Figure S2A**). At extubation, 536 (37.1%) had hemoglobin <9 g/dL and 909 (62.9%) had hemoglobin ≥9 g/dL. Patients with hemoglobin <9 g/dL were less frequently admitted for surgery and had higher SAPS II and SOFA scores at admission, and more frequently had chronic kidney disease (**Table 1**). They also more frequently received red blood cell transfusion within 24 hours before extubation. Post-extubation noninvasive ventilation was more frequently used in patients with hemoglobin <9 g/dL (29.9% vs. 24.4%, p=0.028), whereas high-flow nasal oxygen use was similar between groups (**Table S1**). Among the 332 patients reintubated within 7 days, acute respiratory failure and procedures were the most frequent causes of reintubation (**Table S2**).

The physiological cohort included 128 patients, of whom 40 (31.3%) had hemoglobin <9 g/dL at extubation (**Figure S2B**). Baseline characteristics were broadly similar between hemoglobin groups, although SOFA score at admission was higher in patients with hemoglobin <9 g/dL (**Table S3**). Eight patients (6.3%) were reintubated within 48 hours.

Reintubation and secondary clinical outcomes

The cumulative incidence of reintubation by day 7 was 21.6% (95% CI, 18.2–25.1) in patients with hemoglobin <9 g/dL and 23.5% (95% CI, 20.8–26.3) in those with hemoglobin ≥9 g/dL (**Figure 1**). Hemoglobin <9 g/dL was not associated with reintubation after adjustment for prespecified confounders (adjusted sHR, 0.95; 95% CI, 0.76–1.18; p=0.640), with an adjusted absolute risk difference of −1.0% (95% CI, −5.5 to 3.7) at day 7 (**Table 2A**). The complete multivariable model is reported in **Table S4**. Results were consistent for secondary outcomes, with no significant association between hemoglobin <9 g/dL and reintubation by 48 or 72 hours, 28-day mortality, or ventilator-free days at day 28 (**Table 2B**).

When hemoglobin was analyzed as a continuous variable using Fine–Gray regression, with death before reintubation considered as a competing event, each 1 g/dL decrease in

hemoglobin was associated with an adjusted sHR for reintubation of 0.95 (95% CI, 0.89–1.01; p=0.120) (**Figure S3**). Similarly, when reintubation or death was considered as the composite outcome of extubation failure at day 7, each 1 g/dL decrease in hemoglobin was associated with an adjusted OR of 0.97 (95% CI, 0.91–1.04; p=0.426) (**Figure S4**).

Results for day-7 reintubation remained consistent across sensitivity analyses using alternative adjustment strategies, study populations, and hemoglobin thresholds (**Figure S5A**). Similarly, no consistent association between low hemoglobin and day-28 mortality was observed across sensitivity analyses (**Figure S5B**). Subgroup analyses yielded broadly consistent results, except for an isolated association in patients with coronary artery disease (**Figure S5A**).

Clinical practices

Clinicians extubated patients across a wide range of hemoglobin levels, from 6.0 to 17.9 g/dL, with a median of 9.4 [8.6–10.7] g/dL (**Figure S6**). Hemoglobin levels at extubation decreased over time, from a mean of 9.9 g/dL in 2016 to 9.2 g/dL in 2024, with a Sen's slope of −0.065 g/dL/year (95% CI, −0.145 to −0.007; Mann–Kendall p-for-trend =0.048) (**Figure 2, Table S5**). In contrast, no significant temporal trend was observed in extubation failure at day 7 (Cochran–Armitage p-for-trend =0.229). The proportion of patients receiving RBC transfusion before extubation varied over time (overall RCS p=0.036), without a significant trend across the study period (Cochran–Armitage p-for-trend=0.100). Among transfused patients, the mean number of RBC units administered remained stable (Sen's slope, −0.011 units/year; 95% CI, −0.090 to 0.184; Mann–Kendall p-for-trend =0.754) (**Figure S7, Table S5**).

Inspiratory efforts

In the physiological cohort, respiratory effort increased by 59% from 180+/-93 to 286+/-125 cmH2O.s/min across extubation. Lower hemoglobin levels were associated with a slightly greater increase in inspiratory effort from baseline to after extubation, although associations did not reach statistical significance. For each 1 g/dL decrease in hemoglobin, PTPes/min increased by an adjusted 11.64 $cmH_2O{\cdot}s/min$ (95% CI, −2.82 to

26.10; p=0.114), corresponding to a 7.43% relative increase (95% CI, −3.33% to 18.19%; p=0.174). SwingPes similarly increased by 0.58 cmH_2O (95% CI, −0.03 to 1.18; p=0.061). There was no evidence of nonlinear associations (p for nonlinearity=0.849 and 0.969, respectively) (**Figure 3**). Results were consistent across the other inspiratory effort measures, with the strongest associations observed for PTPes (p=0.05) and relative PTPes (p=0.03) (**Figure S8** and **Figure S9**). These associations were attenuated in robust regression sensitivity analyses, whereas associations for PTPes/min and SwingPes were maintained or strengthened (**Table S6**).

When hemoglobin was categorized at 9 g/dL, the increase in PTPes/min from baseline to after extubation was 134.1 [38.8–200.4] $cmH_2O{\cdot}s/min$ in patients with hemoglobin <9 g/dL versus 74.9 [33.2–158.3] $cmH_2O{\cdot}s/min$ in those with hemoglobin ≥9 g/dL (p=0.200). Similarly, the SwingPes was 7.3 [3.0–11.6] versus 5.4 [2.8–9.6] cmH_2O, respectively (p=0.260). Neither difference was statistically significant, and similar findings were observed using alternative hemoglobin thresholds (7, 8, 10, and 11 g/dL) (**Figure S10**). No significant differences between hemoglobin groups were observed for the other inspiratory effort measures (**Table S7**).

DISCUSSION

Lower hemoglobin at extubation was not associated with a higher risk of reintubation within 7 days, a finding consistently observed across alternative hemoglobin definitions, adjustment strategies, and study populations. Hemoglobin levels at extubation varied widely across patients and decreased over the study period, suggesting increasingly liberal extubation practices regarding hemoglobin level. This decrease was not accompanied by a change in extubation failure over time or in RBC transfusion practices before extubation. Lower hemoglobin levels showed a modest trend toward greater increases in inspiratory effort after extubation, suggesting a potential physiological effect that may be insufficient to translate into a clinically meaningful increase in extubation failure.

Extubation failure remains a major challenge in critically ill patients, occurring in approximately 10–20% of patients[29,30] and being associated with prolonged mechanical ventilation and increased mortality. Identifying potentially modifiable factors at the time of extubation therefore remains important.[23,29,31] However, the role of anemia remains uncertain. Earlier observational studies reported associations between low hemoglobin and extubation failure, but were generally small or restricted to specific populations.[11–13] A 2021 meta-analysis of 18 studies found lower hemoglobin in patients with extubation failure, but the pooled difference was small (0.54 g/dL) and substantial heterogeneity existed across studies.[14] Randomized trials comparing restrictive and liberal transfusion strategies in mechanically ventilated patients provided no evidence that maintaining higher hemoglobin levels improves liberation from mechanical ventilation, although these studies did not specifically evaluate hemoglobin levels at the time of extubation.[15,16] In contrast, our large contemporary cohort specifically evaluated hemoglobin at extubation and found no association with reintubation, consistently across hemoglobin definitions, adjustment strategies, and study populations. Associations observed for individual covariates and in subgroup analyses should be interpreted cautiously, particularly the apparent protective association of anemia among patients with coronary artery disease, given the limited number of events and competing deaths.

To our knowledge, temporal trends in hemoglobin levels at extubation have not previously been described. Clinicians currently receive little guidance regarding an acceptable hemoglobin level for extubation. Earlier weaning recommendations included an "adequate hemoglobin" level, generally ≥8–10 g/dL, among readiness-to-wean criteria,[17] whereas subsequent international guidelines no longer recommended a specific threshold.[18] More recent recommendations have focused primarily on RBC transfusion rather than readiness for extubation. The ESICM guideline suggests a restrictive transfusion threshold of 7 g/dL in patients with prolonged weaning, although based on low-certainty evidence.[19] This evolution toward restrictive transfusion and greater tolerance of anemia may partly explain the progressive decrease in hemoglobin at extubation observed in our cohort.[5,19] Interestingly, this trend was not accompanied by a decrease in RBC transfusion immediately before extubation, suggesting that the progressive reduction in hemoglobin may occur earlier during the ICU stay. Although restrictive transfusion strategies reflect the lack of demonstrated benefit from higher hemoglobin levels and concerns regarding transfusion-related complications,[5,19,32] their implications for extubation remain uncertain. Higher hemoglobin levels at extubation may partly result from preceding RBC transfusion, potentially complicating observational comparisons. In our cohort, however, transfusion was more frequent among patients with hemoglobin <9 g/dL, and excluding patients transfused before extubation did not materially alter the association between hemoglobin and reintubation. The potential for transfusion to improve extubation outcomes in anemic patients, or whether its harms outweigh its benefits, remains uncertain.

Hemoglobin is a major determinant of arterial oxygen content and systemic oxygen delivery.[5] To illustrate, at unchanged oxygen saturation, a decrease in hemoglobin from 10 to 7 g/dL reduces oxygen-carrying capacity by approximately 30%. In healthy individuals, this reduction can be compensated by increased cardiac output and oxygen extraction, allowing oxygen consumption to be maintained despite substantial anemia.[5] Such compensation may be more limited in critically ill patients with reduced cardiovascular or respiratory reserve and inflammation-related alterations in oxygen extraction.[5,33] Supporting the importance of physiological reserve, Schönhofer et al. found that RBC

transfusion reduced minute ventilation and work of breathing in anemic patients with severe COPD, but not in anemic patients without underlying lung disease.[10] This may become particularly relevant during the transition from mechanical ventilation to spontaneous breathing, when respiratory muscle activity and oxygen consumption increase.[6–8] Anemia may therefore increase respiratory effort as a compensatory response to reduced oxygen delivery, which in turn further increases respiratory muscle oxygen demand, potentially creating a vicious cycle.

To our knowledge, this is the first study to directly assess the relationship between hemoglobin level and changes in inspiratory effort across extubation. Lower hemoglobin levels were associated with modestly greater increases in several measures of inspiratory effort, although estimates were imprecise. This physiological signal may be relevant because increased inspiratory effort during spontaneous breathing has been associated with subsequent extubation failure.[34] However, inspiratory effort reflects the balance between respiratory demand and muscle capacity: increased effort may represent an appropriate compensatory response, whereas patients with limited muscle capacity may be unable to increase their effort despite rising demand. Our analyses therefore accounted for baseline (pre-SBT) MIP as a marker of baseline respiratory muscle capacity. Overall, lower hemoglobin may modestly increase the physiological burden of the transition to spontaneous breathing, but this effect alone may be insufficient to translate into a clinically meaningful increase in extubation failure.

This study has several strengths. It addresses an understudied question by combining clinical outcomes, contemporary extubation practices, and respiratory physiology. The large observational cohort included a diverse population of medical and surgical patients from a tertiary-level ICU, while the physiological cohort provided rare direct measurements of inspiratory effort immediately before and after extubation, adding mechanistic insight to the clinical findings.

Several limitations should be acknowledged. First, the observational cohort was derived from a single center, although the physiological cohort included patients from prospective studies conducted in different centers. Second, by studying patients who reached extubation, we could not assess whether anemia or transfusion influenced

earlier decisions to delay extubation or outcomes occurring before extubation, although duration of mechanical ventilation was similar between hemoglobin groups. Residual confounding also precludes causal inference. Third, the relatively high reintubation rate may partly reflect our study design. Inclusion was restricted to patients ventilated for ≥24 hours. The first qualifying ventilation period was retained, such that reintubation after first extubation constituted failure irrespective of subsequent successful extubation. Unplanned extubations, which carry a high risk of reintubation,[35] were included. Reintubation was assessed through day 7. Conversely, the low reintubation rate in the physiological cohort likely reflects highly protocolized planned extubations, with repeated successful spontaneous breathing trials and a mandatory rest period before extubation.

CONCLUSION

In this multidimensional study, hemoglobin levels at extubation decreased over time, reflecting evolving clinical practices toward greater tolerance of anemia, while lower hemoglobin showed a modest trend toward greater inspiratory effort after extubation but was not associated with a higher risk of reintubation. Further studies are needed to determine whether low hemoglobin level represents a modifiable risk factor and whether RBC transfusion can improve or worsen extubation outcomes in selected anemic patients.

LIST OF ABBREVIATIONS

ACLF: Acute-on-chronic liver failure

ALF: Acute liver failure

BMI: Body mass index

CIF: Cumulative incidence function

COPD: Chronic obstructive pulmonary disease

Hb: Hemoglobin

HFNO: High-flow nasal oxygen

ICU: Intensive care unit

MAP: Mean arterial pressure

MIP: Maximal inspiratory pressure

MV: Mechanical ventilation

NIV: Noninvasive ventilation

OSA: Obstructive sleep apnea

PEEP: Positive end-expiratory pressure

PSV: Pressure support ventilation

PTPes: Esophageal pressure–time product

PTPes/min: Esophageal pressure–time product per minute

RBC: Red blood cell

RCS: Restricted cubic spline

RSBI: Rapid shallow breathing index

SAPS II: Simplified Acute Physiology Score II

SBT: Spontaneous breathing trial

SOFA: Sequential Organ Failure Assessment

SwingPes: Esophageal pressure swing

SwingPes/min: Esophageal pressure swing per minute

VFDs: Ventilator-free days

WHO: World Health Organization

DECLARATIONS

Ethics approval and consent to participate

The observational study was approved by the Montpellier University Institutional Review Board (2019_IRB-MTP_05–25). The two physiological trials received ethics approval from the relevant committees (2012-A00294-39 and 2019-A01063-54), and written informed consent was obtained from participants or their representatives. All studies were conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

Research data and other material (eg, study protocol and statistical analysis plan) will be made available to the scientific community, immediately on publication, with as few restrictions as possible. All requests should be submitted to the corresponding author who will review with the other investigators for consideration. A data use agreement will be required before the release of participant data and institutional review board approval as appropriate.

Competing interests

MC reports presentation fees from Duomed. IL reports presentation fees from Viatris and AOP health. CMo reports receiving speaking and lecture fees from Medtronic. GC declares free of fees scientific collaboration with VIATRIS in 2025. ADJ reports receiving consulting fees from Medtronic, Dräger, Viatris and Fisher & Paykel. SJ reports receiving consulting fees from Drager, Duomed, Medtronic, Baxter, Fresenius-Xenios, Mindray, and Fisher & Paykel. No potential conflict of interest relevant to this article was reported for the other authors.

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Authors' contributions

MC and SJ designed the study, MC CMa JP YA CMo and AV collected the data, MC JP and ADJ analyzed the data. All authors were involved in data interpretation. MC CMa JP IL YA, CMo and SJ wrote the manuscript. All authors read and approved the manuscript.

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Table 1: Baseline patient characteristics of the observational cohort

	Overall (n=1445)	Hemoglobin <9 g/dL (n=536)	Hemoglobin ≥9 g/dL (n=909)	p-value	SMD
Female sex	469 (32.5%)	142 (32.3%)	327 (32.6%)	0.964	0.006
Age, years	63 [53-72]	64 [54-72]	63 [52-71]	0.142	0.089
BMI, kg/m^2	26 [22-30]	25 [22-30]	26 [22-31]	0.553	0.079
Surgical admission	671 (46.4%)	238 (40.9%)	433 (50.2%)	0.001	0.187
SAPS II at admission	49 [37-62]	51 [39-63]	48 [36-61]	<0.001	0.199
SOFA at admission	8 [6-11]	9 [6-11]	8 [5-11]	0.029	0.127
Comorbidities					
Obesity (BMI > 30 kg/m^2)	400 (27.7%)	140 (24.1%)	260 (30.2%)	0.013	0.138
Hypertension	527 (36.5%)	218 (37.5%)	309 (35.8%)	0.559	0.034
Coronary artery disease	123 (8.5%)	48 (8.2%)	75 (8.7%)	0.841	0.016
Congestive heart failure	90 (6.2%)	44 (7.6%)	46 (5.3%)	0.108	0.091
Chronic atrial fibrillation	153 (10.6%)	54 (9.3%)	99 (11.5%)	0.214	0.072
Diabetes	343 (23.7%)	150 (25.8%)	193 (22.4%)	0.152	0.080
Stroke	105 (7.3%)	38 (6.5%)	67 (7.8%)	0.433	0.048
COPD	244 (16.9%)	103 (17.7%)	141 (16.3%)	0.545	0.036
Other chronic pulmonary disease	33 (2.3%)	13 (2.2%)	20 (2.3%)	1.000	0.006
OSA	137 (9.5%)	50 (8.6%)	87 (10.1%)	0.392	0.051
Chronic kidney disease	163 (11.3%)	91 (15.6%)	72 (8.3%)	<0.001	0.226
Cirrhosis	413 (28.6%)	175 (30.1%)	238 (27.6%)	0.333	0.055
Current alcohol use disorder	289 (20.0%)	135 (23.2%)	154 (17.8%)	0.015	0.133
Active smoking	288 (19.9%)	124 (21.3%)	164 (19.0%)	0.314	0.057
Cancer	402 (27.8%)	177 (30.4%)	225 (26.1%)	0.081	0.097
Reason for ICU admission					
Coma	122 (8.4%)	42 (7.2%)	80 (9.3%)	0.200	0.075
Cardiac arrest	19 (1.3%)	9 (1.5%)	10 (1.2%)	0.690	0.034
Massive hemorrhage	171 (11.8%)	81 (13.9%)	90 (10.4%)	0.054	0.107
Septic Shock	142 (9.8%)	64 (11.0%)	78 (9.0%)	0.256	0.065
ALF / ACLF	146 (10.1%)	68 (11.7%)	78 (9.0%)	0.122	0.087
Acute kidney injury	21 (1.5%)	14 (2.4%)	7 (0.8%)	0.024	0.127
Acute respiratory failure	349 (24.2%)	144 (24.7%)	205 (23.8%)	0.713	0.023
Postoperative (liver transplant)	115 (8.0%)	27 (4.6%)	88 (10.2%)	<0.001	0.213
Postoperative (other)	275 (19.0%)	99 (17.0%)	176 (20.4%)	0.121	0.087
MV duration before extubation (days)	3 [2-5]	3 [2-6]	3 [2-5]	0.101	0.037
Hemoglobin at extubation, g/dL	9.4 [8.6-10.7]	8.4 [7.9-8.7]	10.4 [9.6-11.4]	<0.001	2.211
RBC transfusion 24h before	262 (18.2%)	123 (21.2%)	139 (16.1%)	0.018	0.130
Fluid balance 24h before, mL	333 [-944-1389]	334 [-1064-1375]	323 [-805-1407]	0.649	0.002
RSBI at extubation, cpm/L	43 [30-58]	43 [28-57]	43 [31-59]	0.344	0.026
MAP at extubation, mmHg	87.0 [78.0-98.0]	86.0 [78.0-97.0]	88.0 [79.0-98.0]	0.106	0.093
Heart rate at extubation, bpm	90.0 [77.0-102.0]	88.5 [78.0-101.0]	90.0 [77.0-103.0]	0.578	0.029
Norepinephrine at extubation	348 (24.1%)	137 (23.6%)	211 (24.5%)	0.747	0.021
SOFA score at extubation	6 [3-8]	6 [3-8]	6 [3-8]	0.092	0.074

Data are presented as median [Q1-Q3] or n (%). P-values were obtained using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. SMD: absolute standardized mean difference

ALF: acute liver failure. ACLF: acute-on-chronic liver failure. BMI: body mass index. COPD: chronic obstructive pulmonary disease. HFNO: high-flow nasal oxygen. MAP: mean arterial pressure. MV: mechanical ventilation. NIV: noninvasive ventilation. OSA: obstructive sleep apnea. RBC: red blood cell. RSBI: rapid shallow breathing index. SAPS II: Simplified Acute Physiology Score II. SOFA: Sequential Organ Failure Assessment.

Table 2A: Association between hemoglobin level at extubation and reintubation within 7 days in the observational cohort

Hemoglobin at extubation	Reintubation by day 7 (95% CI)	Unadjusted sHR (95% CI)	Unadjusted risk difference (95% CI)	Adjusted sHR (95% CI)	Adjusted risk difference (95% CI)
Hb ≥9 g/dL	23.5% (20.8–26.3)	Reference	Reference	Reference	Reference
Hb <9 g/dL	21.6% (18.2–25.1)	0.91 (0.73–1.13)	−1.9% (−6.5 to 2.8)	0.95 (0.76–1.18)	−1.0% (−5.5 to 3.7)

Reintubation probabilities by day 7 are cumulative incidence function (CIF). Death before reintubation was considered as a competing event. Adjusted sHRs were estimated using Fine–Gray competing-risk regression. Adjusted risks and risk differences were obtained by marginal standardization from the adjusted Fine–Gray model, with 95% CIs estimated using 1,000 non-parametric bootstrap resamples.
CIF: cumulative incidence function. sHR: subdistribution hazard ratio. Hb: hemoglobin.

Table 2B: Association between hemoglobin level at extubation and secondary clinical outcomes in the observational cohort

Outcome	Hb <9 g/dL	Hb ≥9 g/dL	Unadjusted estimate (95% CI)	p-value	Adjusted estimate (95% CI)	p-value
Reintubation by 48 h	11.0% (8.4-13.7)	13.1% (10.9-15.3)	0.83 (0.61–1.13)	0.240	0.86 (0.63–1.16)	0.330
Reintubation by 72 h	14.7% (11.7-17.7)	16.9% (14.5-19.4)	0.86 (0.66–1.12)	0.260	0.88 (0.68–1.15)	0.370
Mortality by day 28	50/536 (9.3%)	69/909 (7.6%)	1.24 (0.86–1.79)	0.239	1.16 (0.81–1.68)	0.418
VFDs at day 28	28 [28–28]	28 [27–28]	1.08 (0.85–1.37)	0.519	1.11 (0.87–1.42)	0.389

For reintubation, values are presented as cumulative incidence function (CIF) with 95% CIs, with death before reintubation considered as a competing event. Estimates correspond to subdistribution hazard ratios (sHRs) using Fine–Gray competing-risk regression. Hb ≥9 g/dL was the reference. Mortality is presented as n/N (%) with estimates corresponding to hazard ratios (HRs) obtained using Cox regression, and ventilator-free days as median [Q1–Q3] with estimates corresponding to common odds ratios (ORs) obtained using proportional-odds ordinal logistic regression.
Hb: hemoglobin. VFDs: ventilator-free days

FIGURES LEGEND

Figure 1. Cumulative incidence of reintubation within 7 days according to hemoglobin level at extubation in the observational cohort

Cumulative incidence functions of reintubation within 7 days after extubation according to hemoglobin level <9 g/dL or ≥9 g/dL. Death before reintubation was considered as a competing event. Shaded areas represent 95% confidence intervals. The adjusted subdistribution hazard ratio (sHR) and 95% confidence interval were estimated using Fine–Gray competing-risk regression. Numbers at risk are shown below the graph.

Figure 2: Temporal trends in hemoglobin at extubation and extubation failure at day 7 in the observational cohort

Red and gray lines represent temporal trends in hemoglobin levels at extubation and extubation failure at day 7, respectively, estimated using restricted cubic splines, with shaded areas indicating 95% confidence intervals. Extubation failure was defined as reintubation or death within 7 days after extubation. P-values for trend were obtained using the Mann–Kendall test for hemoglobin and the Cochran–Armitage test for extubation failure.

Figure 3. Association between hemoglobin level at extubation and changes in inspiratory effort from baseline to after extubation in the physiological cohort

Association between hemoglobin level at extubation and changes in (A) esophageal pressure–time product per minute (PTPes/min) and (B) esophageal pressure swing (SwingPes) from baseline to after extubation. Solid lines represent adjusted associations estimated using restricted cubic splines with three knots, with shaded areas indicating 95% confidence intervals (p for non-linearity = 0.849 and 0.969, respectively). Adjusted β coefficients, 95% confidence intervals, and p-values shown in each panel were derived from linear regression models and represent the change in each outcome per 1 g/dL decrease in hemoglobin.

Figure 1. Cumulative incidence of reintubation within 7 days according to hemoglobin level at extubation in the observational cohort

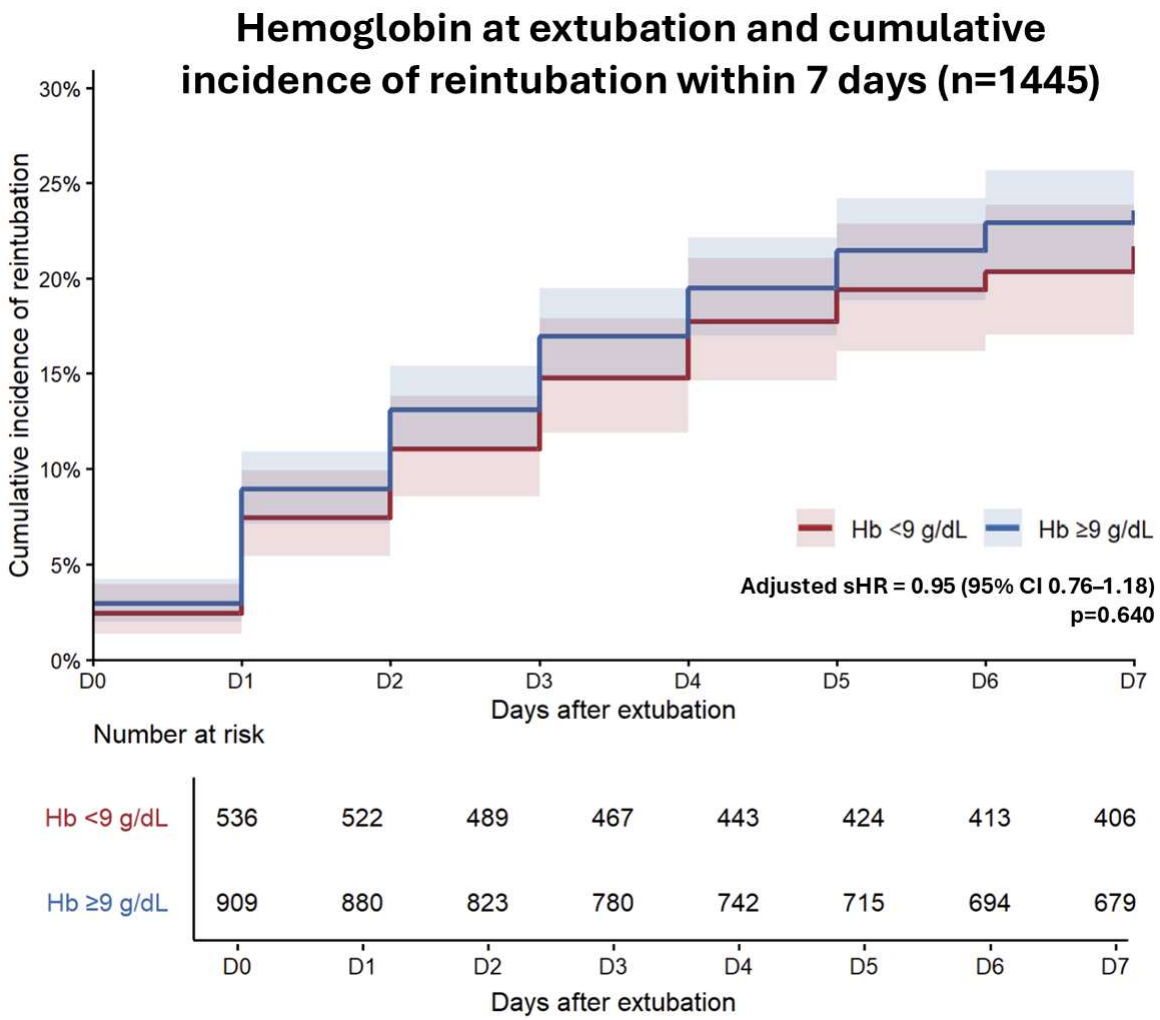


Figure 2: Temporal trends in hemoglobin at extubation and extubation failure at day 7 in the observational cohort

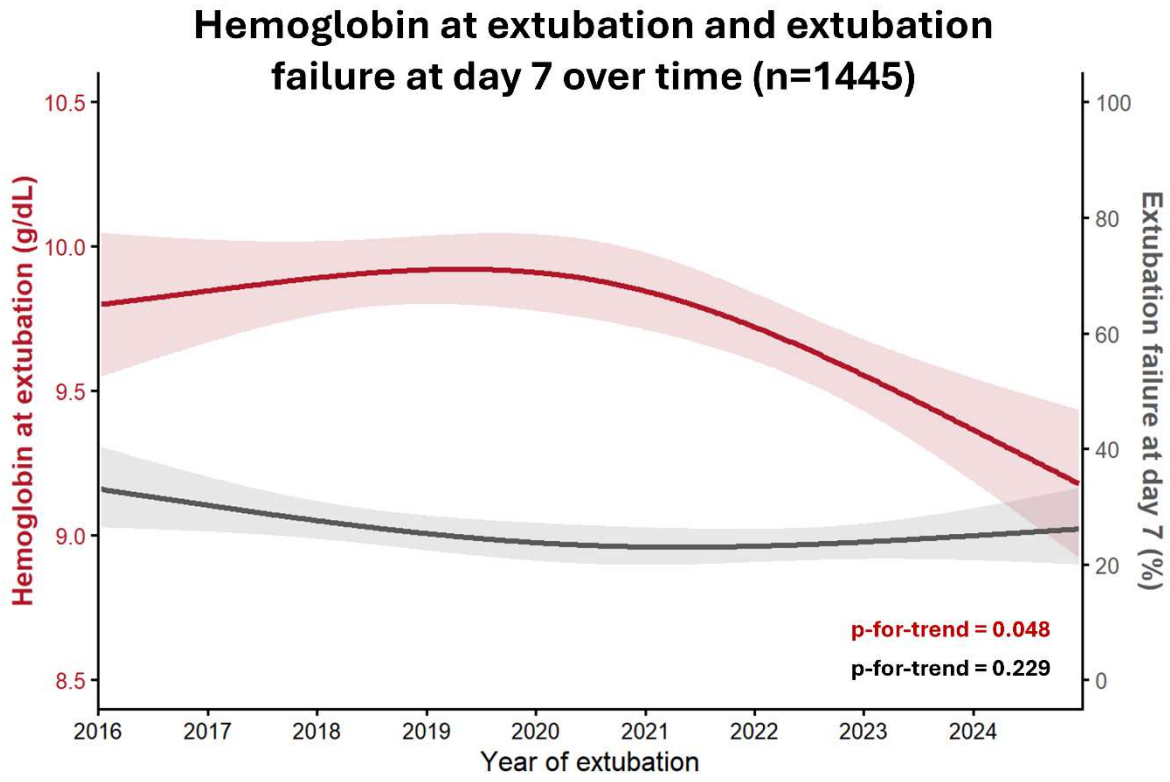
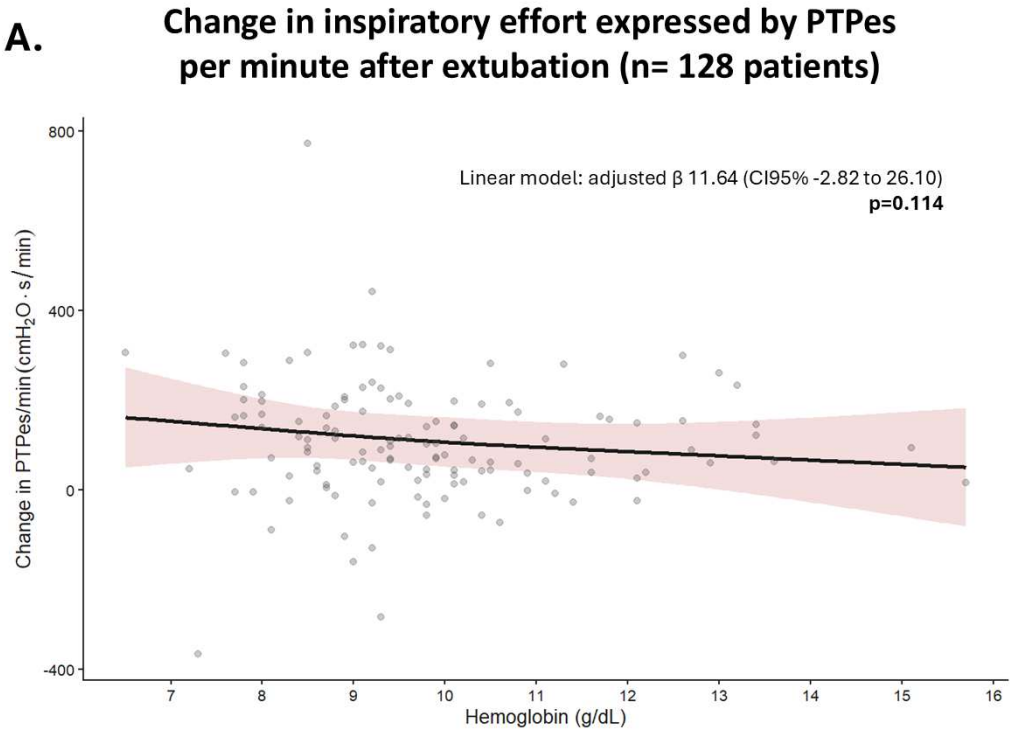
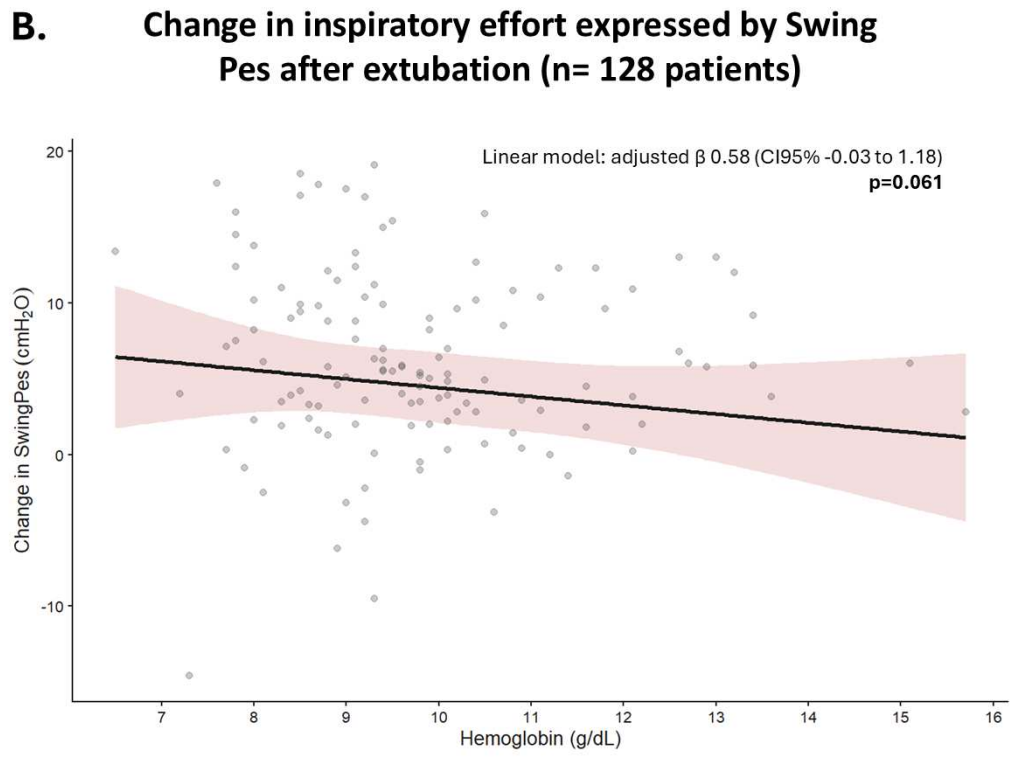


Figure 3. Association between hemoglobin level at extubation and changes in inspiratory effort from baseline to after extubation in the physiological cohort





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