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Assessing safety of mechanical ventilation weaning in patients receiving continuous vasopressors: an emulated target trial

Maxime Fosset

► To cite this version:

Maxime Fosset. Assessing safety of mechanical ventilation weaning in patients receiving continuous vasopressors: an emulated target trial. Human health and pathology. 2023. dumas-04565932

HAL Id: dumas-04565932

<https://dumas.ccsd.cnrs.fr/dumas-04565932v1>

Submitted on 2 May 2024

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UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

THESE

Pour obtenir le titre de
DOCTEUR EN MEDECINE

Présentée et soutenue publiquement
Par

Maxime Fosset

Le 13 Octobre 2023

**Assessing Safety of Mechanical Ventilation Weaning in Patients
Receiving Continuous Vasopressors:
An Emulated Target Trial**

Directeur de thèse : Monsieur le Professeur Boris JUNG

JURY

Président : Monsieur le Professeur Boris JUNG

Premier Assesseur : Monsieur le Professeur Samir JABER

Deuxième Assesseur : Monsieur le Professeur Laurent MULLER

Troisième Assesseur : Monsieur le Professeur Nicolas MOLINARI

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Remerciements

A monsieur le Professeur Jung, depuis notre première rencontre alors que j'étais un externe plein de doutes quant à mon choix de Montpellier comme ville d'internat, jusqu'à ce jour où tu me fais le double honneur de diriger ma thèse et présider son jury, tu n'as cessé de me m'inspirer. Merci de m'avoir transmis ton enthousiasme pour la science et ta curiosité tout au long de mon internat. Mais tu n'es pas seulement un scientifique brillant, tu es aussi un clinicien exceptionnel : depuis que je t'ai entendu prononcer cette simple phrase, je la répète toujours avant de sortir de la chambre d'un patient : « est-ce que je peux faire autre chose pour vous ? » Merci de me rappeler pourquoi je veux faire ce métier. Merci pour ta passion et ta bienveillance, ton sérieux et ta bonne humeur. Merci pour nos lanciers de roulettes du casino pour soumettre à 03 :00 AM, heure française et les ramens bien épicés.

Merci de m'avoir fait découvrir une équipe de recherche incroyable, le climat « tempéré » de Boston et la première université au monde. Merci d'avoir fait pencher la balance pour que je choisisse Montpellier, sans toi je n'aurais jamais pu avancer sur ce parcours et rencontrer tous ces gens formidables. Merci pour ton enseignement, et de me faire l'honneur d'être présent dans mon jury.

A monsieur le Professeur Jaber, j'ai le souvenir très net d'un conseil donné lors de mon passage dans votre service. Vous m'aviez dit qu'en médecine et en recherche, il n'y a que deux choses d'importantes. La première, c'est le patient. La deuxième chose, c'est aussi le patient. Ces mots résonnent en moi depuis à chaque situation difficile à l'hôpital. Merci pour votre enseignement, et de me faire l'honneur d'être présent dans mon jury.

A monsieur le professeur Muller, qui m'a fait découvrir toutes les subtilités de l'échographie en réanimation et qui m'a motivé à poursuivre cette thématique au travers d'un diplôme universitaire. Votre passion pour la médecine et votre bienveillance à l'égard de tous font de vous un véritable modèle pour tous les étudiants. Merci pour votre enseignement, et de me faire l'honneur d'être présent dans mon jury.

A monsieur le professeur Molinari, qui m'accompagne depuis mon master 2, et qui depuis ne cesse de m'impressionner par sa quantité de travail abattu, par la qualité de nos échanges. Merci pour tes encouragements et tout ce que tu fais pour m'aider dans ce parcours. Merci pour ton enseignement, et de me faire l'honneur d'être présent dans mon jury.

A madame la professeure Julie Josse, on dit souvent que discuter avec une personne intelligente vous fait sentir stupide, mais que discuter avec une personne brillante vous fait sentir intelligent. Merci de me donner cette impression, pour tes précieux conseils, et d'avoir enfin réussi à faire signer l'accord pour le mas des moulins. Merci pour ton enseignement, et de me faire l'honneur d'être présent dans mon jury.

A ma famille,

A mon père Laurent, mon modèle de toujours. Merci de m'avoir toujours poussé à faire de mon mieux dans tout ce que j'entreprends. A toujours faire le bien, aider les autres, sans ne jamais rien demander en échange. Je n'oublierais jamais la fierté dans tes yeux le jour où je t'ai annoncé que j'avais réussi le concours et j'allais devenir médecin. J'espère que cette flamme dans tes yeux ne s'éteindra jamais quand tu me regardes.

A ma mère Elisabeth, merci de ton soutien inconditionnel, de tous les sacrifices que tu as faits pour nous. Merci pour tes desserts toujours plus incroyables les uns que les autres, et pour tous les voyages extraordinaires dans notre enfance. Merci de m'avoir fait confiance quand je t'ai dit que je voulais retenter ce concours de première année, je n'aurais jamais pu avoir ce parcours sans toi.

A mon frère Romain, sosie vocal de Dave Grohl et Billie Eilish, spécialiste des étaux, et officiellement « Faster than the speed of love ». Bravo de suivre ta passion jusqu'au bout, je suis très fier de toi. Merci pour toutes nos longues discussions, les cigares, le whisky et les accords de Bm/C#/Em sur une Explorer volume à fond. Merci d'avoir toujours été comme un frère pour moi.

A mes grand-pères, Bernard et Manuel Joaquim, merci pour vos histoires, votre énergie et tout ce que vous m'avez transmis

A mes grand-mères Françoise et Maria-Julia, merci pour votre gentillesse, votre douceur et d'avoir toujours cru en moi

A ma tante Sophie, mon oncle Vincent et Apolline, merci de m'avoir si bien accueilli à Montpellier, pour tout ces moments de détente auprès de la piscine, merci d'être un havre de paix et d'être toujours là pour moi.

A la famille Cadoux, merci pour votre soutien toutes ces années.

A mes collègues,

Tous ceux qui ont croisé ma route et m'ont fait grandir, rire, et continuent de rendre ce monde un peu meilleur.

A l'équipe de réanimation médicale du CHU de Nîmes, au Pr Muller, merci de m'avoir permis de faire mes premières armes, mes premières bêtises, mes premiers succès

A l'équipe du département d'anesthésie-réanimation de St Eloi, au Pr Jaber, au Pr Chanques, à Audrey, Marie, Marion, Moussa, Julie, Yvan, Daniel, Arthur, Marjorie, Chloé B, Chloé R, Mimi, Charlotte, Lucas, merci pour tout ce que vous m'avez appris sur les traitements de la cirrhose, mais aussi ses causes

A l'équipe de pneumologie d'Arnaud de Villeneuve, au Pr Bourdin, Clément, Jean-Pierre, Paul, Quentin, Fred, merci pour les apéros pétanques et l'évaluation de stage mini-golf

A l'équipe de réanimation médicale de Montpellier, au Pr Klouche, Matthieu, Vincent, Philippe, Valérie, Liliane, Noémie, Corinne, Eddine alias BriquetMan, Sonia, Delphine, Cyril, Julie, Vivien, Jonathan, Tiana, merci de votre solidarité pendant l'épidémie, et de tout ce que vous m'avez appris

A l'équipe du département d'anesthésie-réanimation de Lapeyronie, au Pr Capdevila, à Thomas, Blandine, Karim, Camille, Pauline, Geoffrey, Oriane, Hugues l'amateur de légumes, aux petits brookies qui m'ont fait tant rire, le P, le T, le S, le R, et Momo, merci d'avoir rendu ce stage si facile à vivre au quotidien, avec votre bonne humeur, votre énergie et votre sérieux, et pour cette balade nocturne « rafraichissante » aux urgences

A l'équipe de réanimation de Sète, à Soline l'Hokage, Luc, Lucie, Marina, Marina T., Annick, Jean, merci de votre accueil chaleureux et de me permettre de continuer à progresser

Aux internes de MIR du Sud, Antonin, Aude, Didac, Camille, Cécile, Emma, Estelle, Florian, Jonas, Kais, Laëticia, Lucien, Maël, Margot, Rémi, Simon merci de m'avoir accompagné, du Generator à St Etienne en passant par les shooters de sapin, hâte de vous voir tous passer PH 10 ans avant moi

Aux internes de MIR de Montpellier, mes parents Nacim le shreddeur et Sonia le génie, je n'aurais pas pu avoir mieux comme famille d'adoption, à Jonathan, Simon, Jeremy, merci de votre soutien

A toute la promo de MAR de Montpellier 2018, Arthur B, Arthur C, Hugo, Cyprien, Rim, merci de m'avoir accepté malgré ma différence et mon absence de calot de bloc personnalisé

A l'équipe de l'IDESP et de l'INRIA, Hugo, Marie-Félicia, Célia, Ahmed, Rémi, Dominique, Jeff, Laura, Sylvie, Charlotte, Pan, Bénédicte, Imke merci pour vos encouragements et votre aide précieuse

To the CARE team, what a pleasure it was to work with all of you ! Thank you so much for making my time in Boston so enjoyable.

To the Mouse Patrol 02446, Dario and Simone, you are some of the most hard-working, passionate, and brilliant people I've ever met. Hope we'll meet soon for another fancy lab dinner (not too spicy Simone I promise)

Thank you Dario for our amazing scientific discussions, the BBQ, and your everlasting quest to the missing piece!

Merci à Dario et au vrai cerveau du gang NJ pour leur relecture précieuse de ce manuscrit !

Merci à la CEO de m'avoir laissé travailler autant de temps avec son binôme, et de son aide précieuse pour décoder les secrets de 3DSlicer

A mes amis,

A Marc, parce que tu m'a toujours protégé et fait confiance, merci pour ces moments incroyables, merci pour Armadillo, Sol, et ces concerts d'anthologie

A Gaëtan, merci pour cette longue amitié, où chacun sait qu'il peut compter sur l'autre, de dégustation de pain de mie, en écriture de riffs inacceptables jusqu'à cette finale à l'Alhambra

A Kevin, l'unique DJ KevLove, merci pour ton amitié précieuse et ces virées bruxelloises hautement culturelles

Aux apéro-Mojito, vous avez illuminé mon externat, de la plus belle des manières, je serais toujours présent pour vous :

A Réjane, merci d'avoir toujours cru en moi et supporté un défilé de chemises à carreaux aux couleurs qui ferait vomir un daltonien, je t'admire car tu continues de briller comme un Phénix, à toujours te dépasser peu importe les difficultés

Olivier, mon frère de Carcassonne, merci d'avoir toujours mangé mes délicieuses pêches au thon et de toujours me laisser gagner à Magic ou à n'importe quel jeu, félicitations pour avoir enfin eu Poynard. Je t'admire pour ton calme olympien et pour ta solidarité avec tes amis, jamais un BPM ou un mot plus haut que l'autre,

Jalel, mon frère de Carcassonne, créateur des meilleures meringues, meilleures lasagnes au charbon que j'ai jamais mangé, merci de ton oreille attentive, de ton soutien et ton dévouement pour les autres, je t'admire pour tout ce que tu entreprends et réussis

A Marie, qui comme Moïse ouvre les mères en deux, ma valkyrie vengeresse toujours à mes côtés, merci d'être toujours là quand j'ai besoin de toi, mon véritable Patronus sur lequel je peux toujours compter, je t'admire pour ton courage et ta volonté de toujours aller de l'avant malgré les épreuves, je suis très fier de tout ton parcours

Aux théâtreux de la paillasse, chacun d'entre vous est exceptionnel, je suis si fier de vous ! Merci pour tout, Adrien, Anne, Alexandra, Alexandre, Alice, Antoine, Aurélien, Benjamin, Camille, Carine, Guillaume, Gwénaëlle, Jana, Jeanne, Jérémy, Hadrien, Manon, Pauline, Philippine, Sarah, Ségolène, Thomas, Tristan

A toute l'équipe de KRMO et ceux rencontrés pendant l'internat, je n'aurais pas pu rêver mieux,

A Marine, la plus belle âme qui soit, merci pour ta force infinie, ces brunchs dominicaux si doux et ta passion Lana Del Rey. Hâte de t'emmener au Hellfest faire nos doigts de métal

A Hachis, qui m'a divorcé et est parti avec Pépette, mais quel glow-up ! Toujours un plaisir de passer du temps avec toi

A Florence et Sam, merci de m'avoir appris à dire non au Jungle, vous êtes de vrais modèles, ne changez jamais

A Massimo, coloc horloger tic-tic et amateur de boomboom dans les oreilles, j'attends toujours ta participation à Ru Paul's Drag Race, nous aurais tu menti ?

A Marion F. et Elise pour avoir organisé la meilleure crémaillère de Montpellier

A toute la team de la gastro de Perpi,

Righinouche la plus habile des doigts gonflés, une véritable artiste scrotale,

Klem, merci pour ton porte-clé que j'ai gardé précieusement

Au Professeur François, le puits de connaissance sans fond

A Vassilis, l'urgentiste le plus polyvalent de France, peut pratiquer en : mer, montagne, eaux profondes, plongée, Hyrule

A Mérédith, sauveuse de chats et menuisière de génie, hâte de voir ton prochain projet

A Louis, vainqueur du Canigou et triple champion olympique de trampoline, « Mais avant tout»

A Philippe, un mec en Argent(ique), merci pour tous tes cours de photo, j'avoue que je mélange encore parfois l'ouverture et la focale...

A Boris, dénicheur des pires vidéos d'Internet, mais surtout instigateur d'une méthode de mesure quasiment universelle, merci pour ton apport à la science

A Notrepellier, la pire colocation qui n'ait jamais existé, où j'ai haï chaque instant passé à rire, faire les LUCHADORES et transporter des canapés IKEA de taille supérieure à 3 Polos.

A Mathilde, meilleure chanteuse de Blinding Lights de toute la rue Beauséjour. Un timbre de voix à percer le tympan, mais pas d'inquiétude, elle saura parfaitement le redessiner en coupe sagittale de la bouche oesophagienne. Une véritable Fée Fagot, merci d'avoir enchanté ma vie

A Clémence, le sang de la veine, composée à 99% de chips et 1% de ougnougnoulopotitchatlétromignon, ma meilleure alliée pour affronter les zombies et l'ennui

Merci de faire semblant de rigoler à mes blagues depuis tout ce temps, je sais que je ne suis pas si drôle, mais c'est gentil, j'apprécie l'effort. Bien sûr qu'on sera toujours là avec Mathilde, ça signifie tellement pour moi aussi.

A Père Noël, une autre famille,

A Agathe, mi-femme mi-énergie pure, merci de toujours mettre le feu partout où tu passes

Au père Armel, terre de contrastes : le plus social des asociaux, le plus joyeux des déterministes, le mélomane le plus fan d'Alexander Pistoletov ? Merci d'avoir ressuscité après 18h de sommeil pour prouver que les miracles existaient, pour nos discussions où l'on rajoute 12 règles pour la vie, merci d'être toujours là pour moi

A Baptiste D. Sautel, (ou Baptise Sathel ?), qui a mangé le Hito Hito no Mi Model : Homme Parfait, merci pour tes tartes flambées, ta passion pour la menthe puissance 21 et tes soirées 2000's qui font bien remonter le temps

A Chloé, dont le rire résonne partout où elle passe, sur des skis, une planche de surf, de kite ou accrochée à un homard, merci de ne plus jamais me parler de vélo électrique sur une route de chantier

A Irma, dont le sourire prédit toujours une bonne nouvelle, merci pour toutes tes petites attentions et ta bonne humeur permanente, hâte de partager d'autres anniversaires avec toi

A Karl, Superman du monde réel qui tire des rayons pour sauver des vies, le Verstaapen de la punchline, merci de nous avoir fait découvrir ta terre natale

A Lisa, terreur de Tinder et destructrice d'ados de 14 ans, merci de me faire rire et de supporter le Mr Hyde du J21

A Ophélie, a fait trois fois le tour du monde, je pourrais vraiment parler des heures avec toi tant c'est agréable de t'écouter partager tes pensées, merci de ta sincérité, de ton amitié sans faille, et de me laisser te battre au Skull King

A Rémi, où devrais-je dire Brullie, le meilleur paladin du serveur EUW, merci pour ta curiosité sans bornes, ton intérêt pour tous les sujets, et tes slams répétés sur Architects, SATAN

A Sarah, l'aventurière au grand cœur, toujours prête à défendre ses amis, merci de nous montrer la voie à tous, et de nous avoir tant donné envie de traverser la moitié de la planète, ça en valait la peine

A Willy, Roi Midas qui transforme en or ou en TON0 tout ce qu'il touche, depuis que je t'ai vu monter au mat sans frémir au milieu du Pacifique, je sais que tu es un leader né, merci

A Salem, merci pour tes commentaires pertinents sur le flowchat.

A Céline, mon soleil, ma lumière. Rien de tout ça ne serait possible sans ton soutien et ton amour au quotidien. Merci de me montrer ce qui compte vraiment ici-bas. C'est chaque jour un peu plus facile d'écrire notre histoire, chaque jour un peu plus facile de t'aimer. Merci pour tout, je t'aime.

Assessing Safety of Mechanical Ventilation Weaning in Patients Receiving Continuous Vasopressors: An Emulated Target Trial

Authors: TBD

TAKE HOME MESSAGE

- In an emulated target trial, including 6557 medical critically ill patients, weaning mechanical ventilation while receiving low-dose (5 µg/min or less) vasopressors reduced the duration of mechanical ventilation along with an estimated excess number of cases of weaning failure of 30 (95%CI, 4 to 57) per 1000 patients compared to a delayed strategy where vasopressors were discontinued for more than 24 hours.
- Weaning while receiving a dose of vasopressor higher than 5 µg/min increased risk of weaning failure with an estimated excess number of cases of 70 (95%CI, 29 to 111).
- Future randomized trials may evaluate weaning in critically ill patients while receiving low-dose vasopressor strategy.

ABSTRACT

Purpose: Safety of weaning critically ill patients from mechanical ventilation while receiving vasopressor is uncertain. The present emulated trial compares four *a priori* vasopressor discontinuation strategies in critically ill adult medical patients undergoing weaning from mechanical ventilation.

Methods: We performed an emulated trial with consecutive observational data from patients admitted to the intensive care units at Beth Israel Deaconess Medical Center from January 2011 to June 2022. We compared the risk of death or reintubation within 7 days of weaning among four *a priori* defined weaning strategies: delayed weaning after vasopressor discontinuation, early weaning, low-dose, and high-dose vasopressor infusion.

Results: The estimated excess of deaths or reintubations for the early strategy, compared to the delayed strategy, if every patient had followed the early strategy, was 35 (95%CI, 14,8 to 55) per 1000 patients (Risk Difference [RD] = 0.035, 95%CI, 0.015 to 0.055). The estimated excess cases were 30 (95%CI, 4 to 56) per 1000 patients (RD = 0.030, 95%CI, 0.004 to 0.056) for the low-dose strategy in comparison with the delayed strategy. The highest estimated excess case number was in the high-dose vasopressor strategy, with excess cases of 95 (95%CI, 60 to 130) per 1000 patients (RD = 0.095, 95%CI, 0.060 to 0.130).

Conclusions:

In medical critically ill patients, the safest strategy to limit death or reintubation by day 7 was to discontinue vasopressors at least 24h before weaning. Weaning medical critically ill patients with a low-dose of vasopressors was associated with a shorter overall duration of mechanical ventilation and had a modestly increased risk of weaning failure, while the high-dose strategy had the highest risk of weaning failure.

KEYWORDS

Causal Inference, Weaning, Vasopressors, Emulated Target Trial, Causal Forest

INTRODUCTION

Weaning from mechanical ventilation (MV) is an essential component of strategies aimed at optimizing patient outcomes in the intensive care unit (ICU) under mechanical ventilation. Prolonged mechanical ventilation due to delayed weaning can result in complications and prolonged stay in the intensive care unit [1–3].

In contrast, early extubation and potentially resulting weaning failure is commonly associated with a high mortality risk [4,5].

Weaning from MV is a significant area of research [6], resulting in the widespread use of protocols to guide clinical practice [7]. Various protocols recommend weaning patients from MV on minimal or no doses of vasopressors [8]. However, this practice may lead to inadequate or harmful prolongation of MV.

A previous retrospective study reported that weaning MV while receiving high-doses, but not low-doses, was associated with an increased risk of reintubation [9]. Additionally, weaning MV on low-dose vasopressors (defined as a dose lower than 0.1 µg/kg/min) was found to be associated with lower mortality and a shorter length of ICU stay. However, this study was conducted in a mixed surgical and medical population without data on the escalation or resolution phase of septic shock.

To date, there is no consensus on the optimal timing of discontinuing vasopressors and weaning MV, and the safety of weaning medical patients off mechanical ventilation while receiving vasopressor infusions in the ICU remains unclear [10]. Moreover, the safety of weaning right after discontinuing vasopressors infusion has not been studied.

To identify the optimal strategy of vasopressor discontinuation at the time of weaning in adult critically ill medical patients, we conducted an emulated target trial to investigate the total causal effect of four different treatment strategies on the risk of weaning failure by day 7. We hypothesized that weaning while receiving a low-dose of vasopressor would be the strategy with the lowest risk of weaning failure.

METHODS

Study population and data collection

We analyzed consecutive patient cases admitted to the ICUs (80 beds) of Beth Israel Deaconess Medical Center (BIDMC), a tertiary healthcare network in Boston, Massachusetts, USA, from January 2011 to June 2022. Deidentified data were extracted from the electronic healthcare records. Patients with full code order, admitted to the ICU, undergoing MV for more than 12 h, receiving vasopressors at any point during MV, and having a spontaneous mode of ventilation before weaning were eligible for inclusion. Patients with do not reintubate order during their stay, who died the day of end of MV or with an history of surgery in the 7 days prior or after the end of MV were excluded from the analysis.

To better assess the patient transition from lung protective ventilation to a support mode of ventilation [11], the mechanical ventilation period was divided into two phases: an initial phase of ventilation, in which both controlled modes or assisted modes of ventilation were used, and a weaning phase of ventilation, defined as the first period of continuous assisted ventilation mode that ended with the extubation of the patient (E-Figure1). Respiratory parameters were extracted for both periods.

This study was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (protocol number: 2023P000649) and the requirement for informed consent was waived. This study is compliant with the STROBE guidelines for reporting observational studies [12], as guidelines for reporting emulated target trials are under development [13].

Study design

Target Trial Framework

We used the target trial emulation framework [14,15], which involves specifying the protocol for a hypothetical randomized controlled trial and then emulating this target trial using the available observational data. The components of the target trial and its emulation are summarized in E-Table 1, as described by Dickerman et al [16].

Eligibility Criteria and Treatment Strategies

The emulated trial employs the same inclusion and exclusion criteria as the target trial. The BIDMC weaning ventilation protocol precludes weaning in case of an active uptitration of vasopressors, but weaning is at providers discretion in any other situation regarding the vasopressors dose (E-Table 2).

In this trial, we compared four *a priori* strategies based on time from vasopressor discontinuation to weaning or dose of vasopressors at the time of weaning: (1) the delayed strategy: weaning at any time if vasopressors have been discontinued for more than 24h; (2) the early strategy: weaning at any time if vasopressors have been discontinued for 24h or less, (3) the low-dose strategy: weaning at any time while patients are receiving a vasopressor dose of 5 µg/min or less; and (4) the high-dose strategy: weaning at any time while patients are receiving a vasopressor dose greater than 5 µg/min.

Time Zero

For the emulated trial, we set time zero as the time point at which mechanical ventilation was weaned following a continuous period of only assisted mode ventilation. To allocate patients to each treatment strategy, we considered whether they received vasopressor infusions at that time, as well as the total vasopressor dose in the norepinephrine-equivalent dose [17] or the time since their last infusion was discontinued.

Outcomes

The outcomes were defined *a priori*. The primary outcome was weaning failure by day 7 after weaning, defined as reintubation or death. [18]

Secondary outcomes included in-hospital mortality, 30-day mortality, 28-day ventilator-free days [19], length of ICU stay, length of hospital stay, and total mechanical ventilation duration after the first episode.

Causal model and data analysis

Primary analysis

To assess the causal effect of each of the four treatment strategies for an individual, we need to estimate the contrast of the counterfactual outcomes of each treatment strategy, i.e., what would have been the outcome of that individual if they had received the treatment versus if they had not received the treatment.

Typically, we cannot estimate individual causal effects because for each individual, only one of the counterfactual outcomes is observed. Nonetheless, we can estimate the average causal effects here as a causal risk difference; the difference in the mean outcome had everyone been treated with one strategy minus the mean outcome had everyone been treated with another strategy.

As no relevant randomized trial is available to answer our question of interest, we need to analyze observational data.

To use real-world data to make inferences, we must satisfy three main assumptions as the treatment assignment is not randomized. [20]

1) *Positivity*: the probability of receiving every treatment value for each individual must be positive; that is, greater than zero. Consequently, observational data cannot be used to emulate treatment strategies that do not exist in the real world: the target trial must be a pragmatic trial.

2) *Consistency*: the values of treatment strategies under comparison correspond to well-defined interventions that, in turn, correspond to the versions of treatment in the data.

3) *Exchangeability*: for an observational study to be seen as a conditionally randomized experimental study, we must assume exchangeability in our population. In a randomized controlled study, distribution of covariates in each treatment group are identical, which is not true in an observational study. To address these confounding issues, we identified a sufficient adjustment set of covariates related to both the treatment and the outcome, based on *a priori* knowledge and clinical expertise by constructing a causal direct acyclic graph (E-Figure 2, www.dagitty.net [21]), and collected the variables according to our proposed hypothesis of the data-generating mechanism.

To estimate the causal effect and adjust for confounding, we used a double robust machine-learning algorithm introduced by Athey et al. [14], called the causal forest.

This algorithm is derived from the random forest algorithm, an ensemble machine learning method [15], which uses a combination of predictions made by individual trees, built on a random subset of data.

Causal trees use different criteria than those usually employed, such as the mean square error, to maximize the heterogeneity of the treatment effect at each split.

The causal forest is grown to estimate weights, for each observation integrating the difference between the observed outcome and its predicted effect and the propensity score while optimizing an objective function called R-learner [16].

Finally, this specific approach to growing the forest and the type of sample splitting used, called honesty [17], allows for an unbiased estimation of the conditional average treatment effect (CATE), or the expected difference in potential outcomes for individuals with the same covariate values if they were to receive a specific treatment strategy versus receiving another.

The average treatment effect, or the treatment effect over the entire population, is estimated with the standard error through augmented inverse propensity weighting (AIPW), a double robust estimator [18].

In summary, the CATE allows us to explore the heterogeneity of the treatment with respect to the covariate, while the ATE gives the average treatment effect for the entire population and can be used if one wants to apply one unique treatment strategy.

Secondary analyses

Heterogeneity of treatment effect

To summarize the output of complex algorithms, such as causal forest, we created three subpopulations of patients based on the tercile of the predicted conditional treatment effect, as previously described by Wager et al. [22]

We estimated the ATE for each group and tested whether the three subgroups had different average covariate levels across the terciles of estimated CATE.

This approach allowed us to compare the ten most important covariates to represent the heterogeneity between individuals with a high and low treatment effect.

Sensitivity analyses and missing data

Several methods of confounding adjustment were used in this emulated trial to compare the different approaches for estimating the average causal effect of treatment in terms of risk differences: inverse probability of treatment weighting with entropy balancing, g-formula, and double robust methods. The details are provided in *the supplementary material*.

Primary analysis used the causal forest algorithm which directly incorporate a way to handle missing values through the missing incorporated attribute criterion. This method has been showed to generally performs at least as well as multiple imputation and it is designed for forest based methods [23].

As a sensitivity analysis, missing data for the selected covariates were imputed with a single imputation algorithm, using an iterative Factorial Analysis for Mixed Data model, which allows imputation to consider similarities between both individuals and relationships between variables [24,25], and the methods were applied to the imputed dataset.

The bootstrap method with 1000 samples was used to estimate the 95% confidence intervals for relevant estimates. Analyses were performed using Stata (version MP 16.0, StataCorp LLC, College Station, TX, USA) and R Statistical Software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) with the grf package [26].

RESULTS

Study population

A total of 6657 patients were included in this analysis after excluding those who underwent surgery within 7 days prior to or after intubation (Figure 1). The analysis excluded patients who had a code status of "Do Not Resuscitate," "Do Not Intubate," or "Comfort Measures Only" before weaning, or who died on the day of the end of MV.

Patient characteristics at baseline are summarized in Table 1.

Of the 6657 included patients, 2745 (41.2%) followed the delayed strategy, with an average duration of initial and weaning phases of MV of 211 h, whereas 2257 (33.9%) followed the early strategy, with an average duration of early and weaning phases of MV of 73 h. For the strategies involving continuous administration of vasopressors, 1036 (15.6%) patients received a low-dose of vasopressors at weaning, with an average duration of initial and weaning phases mechanical ventilation of 80 h. Additionally, 619 (9.3%) patients were extubated while receiving a high-dose of vasopressors, with an average duration of initial and weaning phases MV of 78 h. The overlap and positivity assumption were respected, with no probability of being treated too close to zero or one, ensuring that we can meaningfully compare patients in each treatment strategy as

each patient has a non-null probability of being in every strategy (E-Figure 3). An acceptable balance between the main covariates included in the model was obtained after weighting by the causal forest (E-Figure 4).

Primary analysis

The delayed ventilation weaning strategy presented the lowest risk of the primary composite outcome of weaning failure defined as death or reintubation by day 7, compared to the other strategies, all of which exhibited a positive risk difference (RD). (Figure 2)

The estimated excess cases of death or reintubation for the early strategy had every patient followed this strategy compared to had everyone followed the delayed strategy was 35 (95%CI, 14.8 to 55) per 1000 patients (RD = 0.035, 95% CI, 0.0148 to 0.055).

For the low-dose strategy, the estimated excess cases were 30 (95% CI, 4 to 56) per 1000 patients (RD = 0.030, 95% CI, 0.004 to 0.056). The highest estimated excess cases of death or reintubation by day 7 was in the high-dose vasopressor strategy, with a number of excess cases of 95 (95% CI, 60 to 130) per 1000 patients (RD = 0.095, 95% CI, 0.060 to 0.130).

For the early and low-dose vasopressor strategies, this elevated risk was moderated through the risk of reintubation, but not through the risk of death. The estimated excess cases of reintubation by day 7 had every patient followed the early or low-dose vasopressor strategies compared to had everyone followed the delayed strategy was 23 (95% CI, 5 to 41) and 28 (95% CI, 3 to 53) per 1000 patients, respectively (Figure 2). The excess risk for these two strategies compared to the delayed strategy was not statistically significant for the risk of death, with an estimated number of cases of 12 (95% CI, -3 to 25) and 8 (95% CI, -8 to 24).

The estimated excess cases of reintubation and death had every patient followed the high-dose of vasopressor strategy compared to everyone had followed the delayed strategy was 70 (95% CI, 29 to 111) and 64 (95% CI, 39 to 90) per 1000 patients, respectively.

Table 2 presents the weighted averages of the secondary outcomes for each strategy, with the weights estimated with the primary outcome model.

The mortality rate both in-hospital and by day 30 after weaning remained consistent across all four treatment strategies (Table 2). Similarly, there was no disparity in the total duration of mechanical ventilation, number of ventilator-free days by day 28, length of ICU or hospital stay among the four strategies.

Secondary analyses

Conditional Average Treatment Effect (CATE) estimates

Three data-driven groups of patients, defined by their ranking in terms of predicted CATE, were generated according to the terciles. Group Q1 was defined by a non-statistically significant risk difference (ATE = -0.008, 95%CI, -0.037 to 0.021). Group Q2 was defined as low excess risk (ATE=0.040, 95%CI, 0.003 to 0.077), and group Q3 was defined as high excess risk (ATE=0.067, 95%CI, 0.026 to 0.108). (E-Figure 5)

The average values of the covariates for each group for the ten most important covariates in terms of variance are shown in Figure 3.

The group of patients Q1, without increased risk for the primary outcome, was defined by a younger age, a higher PaO₂ and FiO₂ set during the weaning period of ventilation, a lower dose of vasopressor at the time of weaning, and a shorter duration of the initial phase of mechanical ventilation.

Sensitivity analysis

The average treatment effect of each strategy compared to the delayed discontinuation strategy (vasopressors discontinued for more than 24 h at the time of weaning) for the primary outcome as estimated by different parametric methods as multivariable logistic regression and double robust machine learning methods is available in Supplemental (E-Figure 6). The estimated risk differences were consistent across all methods used, with an average low risk difference for the early weaning strategy and a high risk difference for the high-dose strategy.

For the low-dose strategy, most of the methods used showed a risk difference close to zero.

DISCUSSION

Contrary to our main hypothesis, the present emulated trial shows that the weaning strategy with the lowest risk of weaning failure in a medical critically ill population is the delayed discontinuation strategy in which vasopressors are discontinued for more than 24h before weaning. The highest risk strategy is the high-dose strategy, in which vasopressors are administered at doses greater than 5 $\mu\text{g}/\text{min}$, which carries an increased risk of reintubation or death, with an estimated number of excess cases of 10 per 1000 patients (95%CI, 6 to 13) compared to the delayed strategy.

Our results are concordant with a previous study by Zarrabian et al. [9], who showed a higher risk of reintubation and death with a vasopressor dose greater than 0.1 $\mu\text{g}/\text{kg}/\text{min}$, which may probably preclude the use of this strategy in a medical population.

Our study adds to this by demonstrating that the excess risk in the early discontinuation strategy (in which vasopressors are discontinued for less than 24 h before weaning) and the low-dose strategy (in which vasopressors are administered at dose less than 5 $\mu\text{g}/\text{min}$) is mainly driven by the excess risk of reintubation and not death with a modest effect size (Figure 2), and no significant effect on longer-term exploratory outcomes (Table 2).

In an effort to explore the heterogeneity of the treatment effect, this emulated trial shows that there is no excess risk of weaning failure and a shorter duration of MV in younger patients with higher values of arterial pressure in oxygen, lower doses of vasopressors, and shorter duration of MV in the initial phase of ventilation. We found an increased risk of weaning failure across all causal inference methods (Figure 2, E-Figure 6) in patients in whom vasopressors were discontinued less than 24h before weaning (“early strategy”). In the present emulated trial, we enrolled high risk medical patients with a high Elixhauser comorbidity score and with a 40% rate

of congestive heart failure and chronic respiratory disease (Table 1). Extubating these patients shortly after having discontinued the vasopressors may have exposed them to a suboptimal weaning process including weaning induced pulmonary edema due to concomitant switch from positive to negative pressure ventilation and cardiovascular changes. [10,27,28]

We observed that patients within the highest risk of weaning failure group received higher doses of vasopressors during the first four days of MV. (Figure 3)

Although there is a lower risk of weaning failure in the delayed vasopressor discontinuation strategy, it is associated with a longer duration of MV (Table 1), potentially balancing the overall benefit relevance of that strategy (Figure 3).

Every factor that can shorten the initiation of weaning, such as early weaning with low-dose vasopressors, might improve weaning success in selected patients. In a prospective observational multicenter study for instance, Pham et al. showed that only 65% of patients were successfully weaned from ventilation on day 90 and that delayed initiation of weaning was associated with weaning failure. [31] Future randomized controlled trials may focus on the safety of weaning patients with low-dose vasopressors at the time of weaning and its effect on the total duration of MV.

The present emulated trial has several limitations. First, our results to infer causation are only as robust as the unconfoundness assumption that we made, despite our efforts to include and control for every potential confounder available. We used double robust machine learning methods to gain robustness against misspecification of one of the two models, the propensity model, or the outcome model. The target trial emulation allows us to get as close as possible to a randomized controlled study by avoiding several pitfalls of observational studies [32], and the machine learning method used can better capture complex patterns or relationships in the large space of available covariates [33]. Second, our emulated trial was specifically designed to answer the question on the causal treatment effect of the four strategies on the primary composite outcome

of reintubation or death by day 7. Therefore, the interpretation of secondary outcomes is exploratory.

Third, although the patients were admitted to different ICUs in the same hospital, this emulated trial was conducted in a single large academic hospital and may lack generalizability.

We believe that our findings provide important insights, as this is the largest available cohort of medical critically ill patients, with access to most of the variables in our confounder model with high granularity of data and a study design aimed at estimating a causal treatment effect.

Our findings have implications for future randomized controlled trials to ensure a good equipoise. Despite a small effect on the risk of reintubation, the low vasopressor dose strategy may be considered as a potential best deal strategy since it was associated with a much shorter duration of mechanical ventilation than the delayed vasopressor discontinuation strategy. These future trials may focus on strategies in which the dose of vasopressors at the time of weaning is minimal and avoid a short delay between the discontinuation of vasopressors and weaning. Identifying optimal management of vasopressors during the period of weaning from mechanical ventilation should be seen as a global effort to personalize care, as this could provide tools to select patients who are eligible for early weaning of MV, to reduce harm of prolonged MV [34].

CONCLUSION

In conclusion, the present emulated trial shows that the weaning strategy with the lowest risk of weaning failure is the delayed discontinuation strategy in which vasopressors are discontinued for more than 24h before weaning, and not the low-dose strategy.

Nonetheless, there is heterogeneity in the effect of the low-dose strategy, which may be safe in selected patients. The high-dose strategy should be avoided as it may lead to an increased risk of weaning failure.

This emulated trial may inform future randomized trials, that could assess the potential reduction in the duration of mechanical ventilation with the low-dose vasopressor strategy.

STATEMENTS AND DECLARATIONS

FUNDING

No financial support was specifically received for this study.

Maxime Fosset has been funded through a grant provided by the MUSE (Montpellier University School of Excellence Young Investigators PhD award 2022) foundation.

This work/project was publicly funded through ANR (the French National Research Agency) under the "Investissements d'avenir" programme with the reference ANR-16-IDEX-0006 »).

All researchers, both external and internal, had full access to all of this study's data, statistical reports, and tables, and therefore take responsibility for the integrity of the data as well as the accuracy of data analysis and reporting.

DATA SHARING

Requests of qualified researchers trained in human subject research and confidentiality to access additional documents; the dataset may be sent to the corresponding author.

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FIGURES

Figure 1. Flowchart

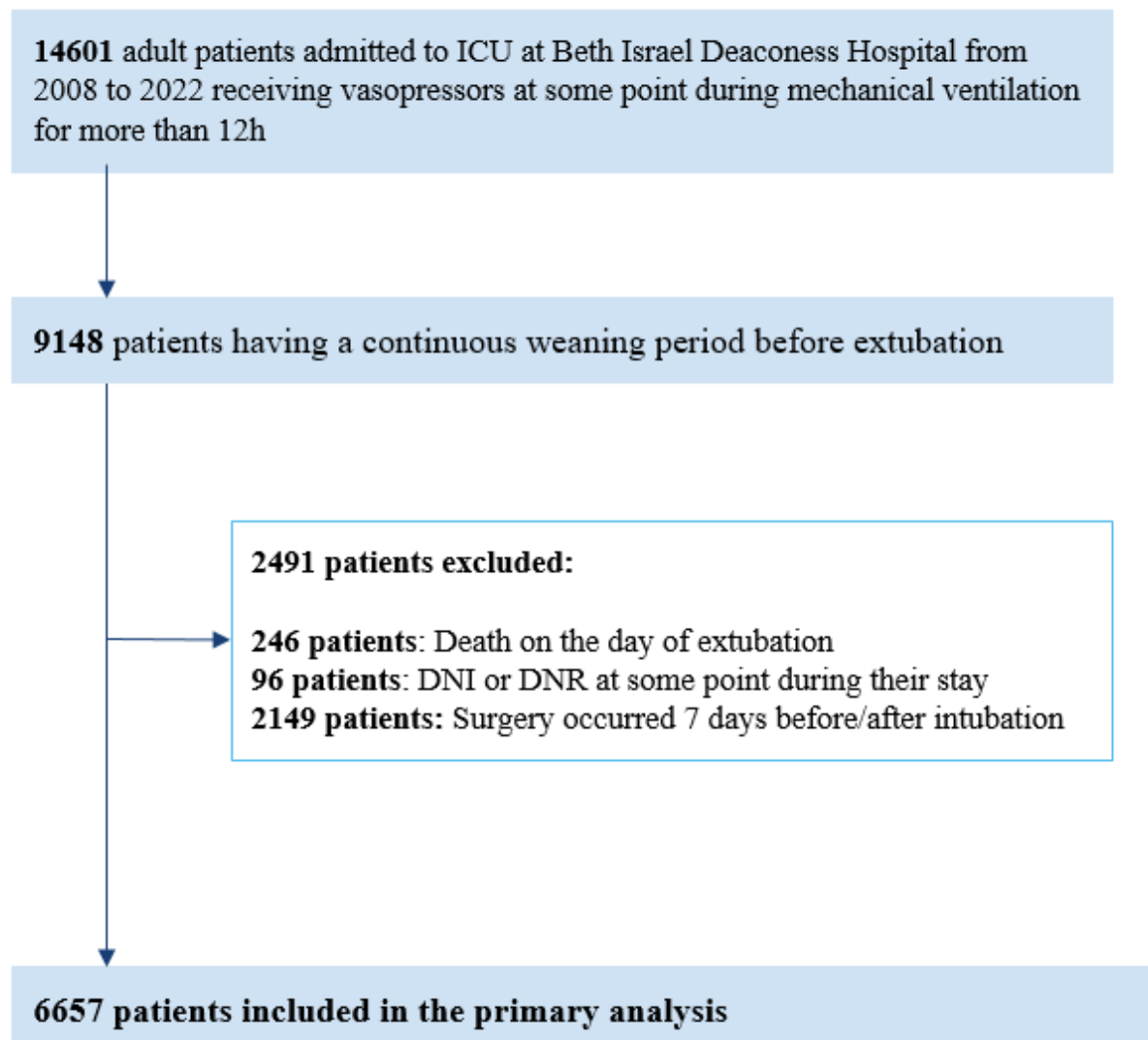


Figure 2. Comparison of the three vasopressors discontinuation strategies to the delayed strategy (baseline) in term of risk difference, with 95% confidence interval

Average treatment effect of the three strategies compared to the delayed strategy (baseline) on the primary composite outcome (weaning failure defined as death or reintubation by day 7):

Delayed strategy (baseline): vasopressors discontinued for more than 24 hours at the time of weaning

Early strategy: vasopressors discontinued for 24 hours or less at the time of weaning

Low-dose strategy: vasopressors at a dose of 5 µg/min or less at the time of weaning

High-dose strategy: vasopressors at a dose greater than 5 µg/min at the time of weaning

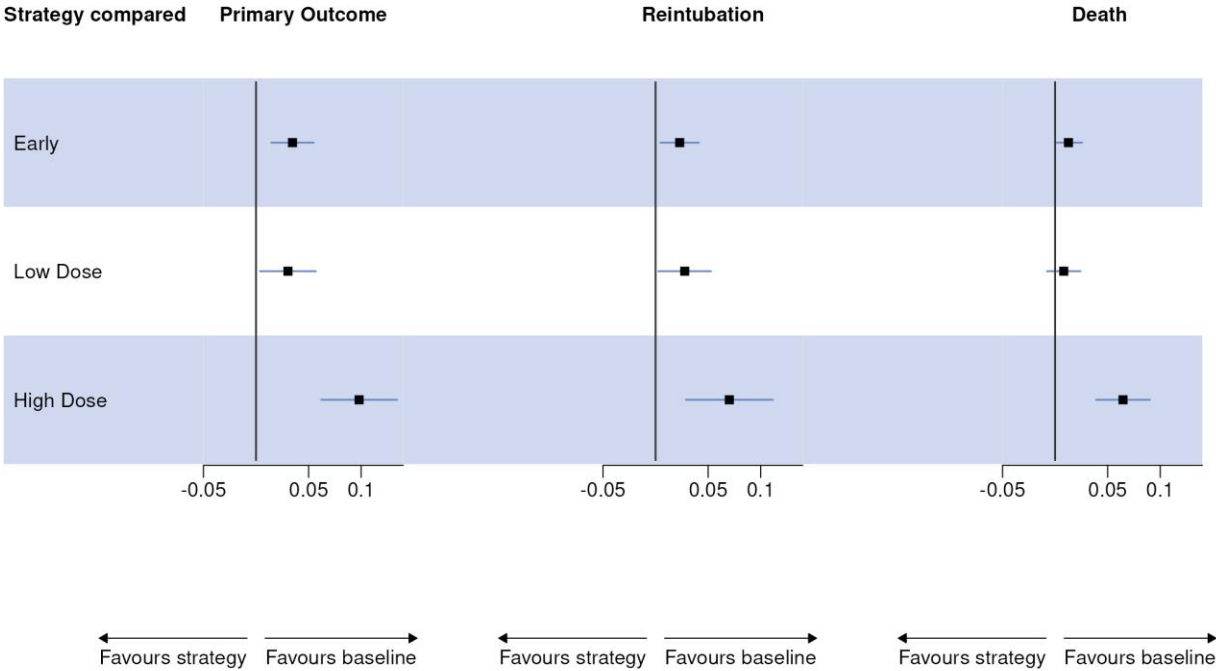


Figure 3. Heatmap of average value of covariates according to tercile of conditional average treatment effect (CATE) group

The ten most important variables in term of their variation are shown. The variation of a covariate reflects how much the average value of a covariate changes relative to its overall variation in the data.

Colors are assigned according to where the subgroup’s mean value lands on the standardized empirical distribution of its variable: $(x - \text{mean}(x))/\text{sd}(x)$

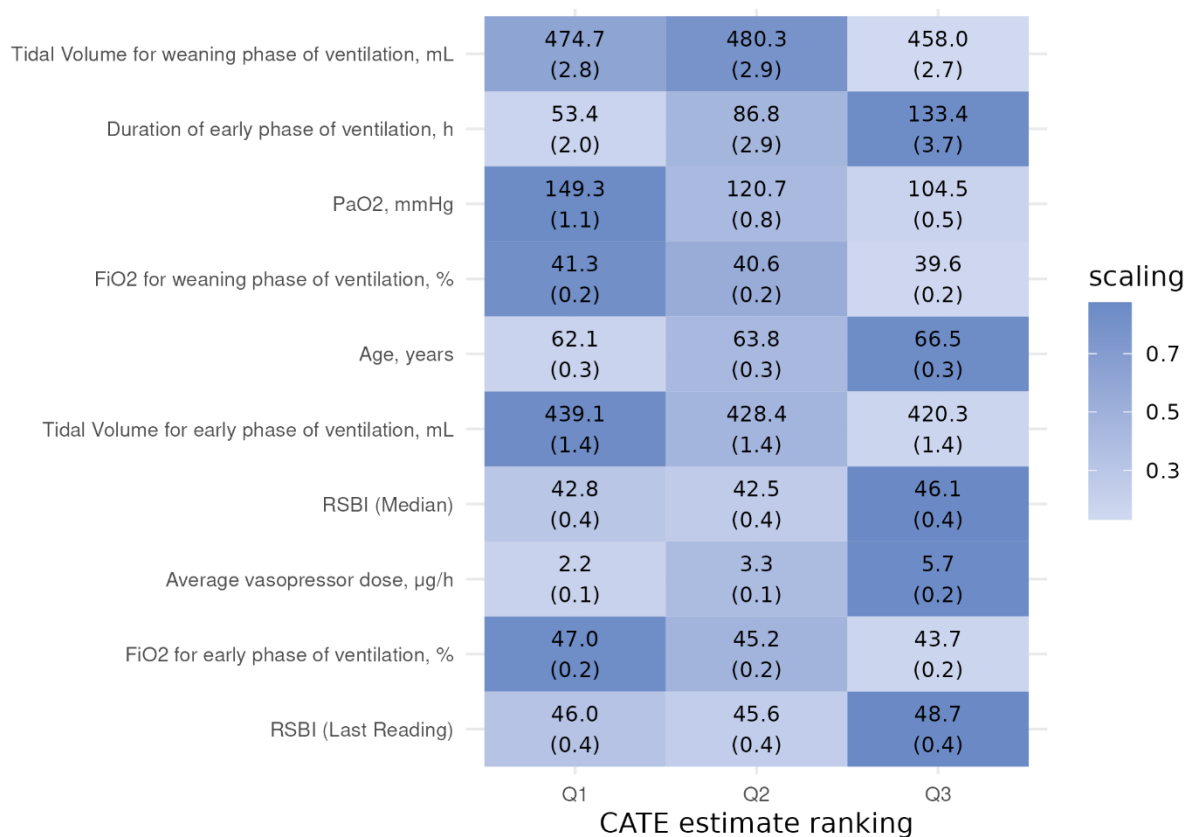


Table 1. Demographic and physiologic characteristics of the patients

Characteristic	Overall, N = 6657 ¹	Vasopressors discontinued for more than 24 hours at the time of weaning, N = 2745 ¹	Vasopressors discontinued for 24 hours or less at the time of weaning, N = 2257 ¹	Vasopressors at a dose of 5 µg/min or less at the time of weaning, N = 1036 ¹	Vasopressors at a dose greater than 5 µg/min at the time of weaning, N = 619 ¹
Baseline characteristics at admission					
Age, years	64 ± 15	62 ± 16	65 ± 15	65 ± 15	65 ± 14
Sex					
Female	2707 / 6657 (41)	1157 / 2745 (42)	911 / 2257 (40)	424 / 1036 (41)	215 / 619 (35)
Male	3950 / 6657 (59)	1588 / 2745 (58)	1346 / 2257 (60)	612 / 1036 (59)	404 / 619 (65)
Body Mass Index, kg/m ²	29 ± 8	30 ± 9	29 ± 7	28 ± 7	30 ± 8
Total Elixhauser Score	21 ± 13	21 ± 13	20 ± 13	23 ± 13	24 ± 13
Congestive Heart Failure	2709 / 6643 (41)	942 / 2740 (34)	936 / 2253 (42)	507 / 1032 (49)	324 / 618 (52)
Chronic Pulmonary Disease	2363 / 6643 (36)	954 / 2740 (35)	798 / 2253 (35)	375 / 1032 (36)	236 / 618 (38)
Obstructive Sleep Apnea Syndrome	1097 / 6657 (16)	453 / 2745 (17)	353 / 2257 (16)	170 / 1036 (16)	121 / 619 (20)
Obstructive Lung Disease	2072 / 6657 (31)	852 / 2745 (31)	704 / 2257 (31)	319 / 1036 (31)	197 / 619 (32)
Restrictive Lung Disease	381 / 6657 (6)	166 / 2745 (6)	124 / 2257 (6)	57 / 1036 (6)	34 / 619 (6)
Smoking Status	3178 / 6657 (48)	1207 / 2745 (44)	1127 / 2257 (50)	507 / 1036 (49)	337 / 619 (54)
Disease severity at admission					
Total Sequential Organ Failure Assessment (SOFA) Score	11 ± 3	11 ± 3	11 ± 3	11 ± 3	12 ± 3
Overall APACHE Score	25 ± 7	26 ± 7	25 ± 6	24 ± 6	26 ± 6
Fluid balance for the first 4 days of MV, mL	-1164 ± 6303	-1562 ± 6731	-1024 ± 5700	-1060 ± 6024	-16 ± 6721
Average vasopressor dose in NED for the first 4 days of MV, µg/min	3.72 ± 6.03	3.55 ± 6.13	2.93 ± 5.08	3.92 ± 5.78	7.07 ± 7.82

Characteristic	Overall, N = 6657 ¹	Vasopressors discontinued for more than 24 hours at the time of weaning, N = 2745 ¹	Vasopressors discontinued for 24 hours or less at the time of weaning, N = 2257 ¹	Vasopressors at a dose of 5 µg/min or less at the time of weaning, N = 1036 ¹	Vasopressors at a dose greater than 5 µg/min at the time of weaning, N = 619 ¹
Respiratory characteristics and parameters during initial phase of mechanical ventilation					
Initial Phase Ventilation Duration, hours	91 ± 142	147 ± 184	51 ± 79	55 ± 90	52 ± 81
Median PaO ₂ /FiO ₂ Ratio					
≥ 400	1108 / 4895 (23)	386 / 2024 (19)	429 / 1684 (25)	184 / 741 (25)	109 / 446 (24)
300-399	908 / 4895 (19)	336 / 2024 (17)	329 / 1684 (20)	150 / 741 (20)	93 / 446 (21)
200-299	1364 / 4895 (28)	548 / 2024 (27)	470 / 1684 (28)	210 / 741 (28)	136 / 446 (30)
100-199	1164 / 4895 (24)	543 / 2024 (27)	374 / 1684 (22)	155 / 741 (21)	92 / 446 (21)
< 100	351 / 4895 (7)	211 / 2024 (10)	82 / 1684 (5)	42 / 741 (6)	16 / 446 (4)
Median Positive End-Expiratory Pressure (PEEP), cmH ₂ O	6.8 ± 2.7	7.3 ± 3	6.4 ± 2.4	6.3 ± 2.3	6.4 ± 2.3
Median Driving Pressure, cmH ₂ O	11.8 ± 3.2	12.1 ± 3.2	11.6 ± 3.2	11.6 ± 3.1	11.6 ± 3.0
Median Tidal Volume, mL	429 ± 66	423 ± 67	434 ± 66	430 ± 67	438 ± 61
Median Respiratory Rate, breaths/min	19 ± 4.5	19.5 ± 4.8	18.6 ± 4.4	18.4 ± 4.2	19.1 ± 4.1
Median Fraction of Inspired Oxygen (FiO ₂)	45 ± 11	45 ± 10	46 ± 11	46 ± 11	47 ± 12
Respiratory characteristics and parameters during weaning phase of mechanical ventilation					
Total SOFA Score	10 ± 4	10 ± 3	10 ± 3	11 ± 3	12 ± 3
Weaning Phase Ventilation Duration, hours	40 ± 59	64 ± 76	22 ± 31	25 ± 39	26 ± 40
Median PaO ₂ /FiO ₂ Ratio					
≥ 400	586 / 4023 (15)	221 / 1559 (14)	195 / 1391 (14)	104 / 653 (16)	66 / 420 (16)
300-399	1065 / 4023 (26)	374 / 1559 (24)	366 / 1391 (26)	202 / 653 (31)	123 / 420 (29)
200-299	1517 / 4023 (38)	591 / 1559 (38)	531 / 1391 (38)	228 / 653 (35)	167 / 420 (40)
100-199	803 / 4023 (20)	344 / 1559 (22)	285 / 1391 (20)	112 / 653 (17)	62 / 420 (15)
< 100	52 / 4023 (1)	29 / 1559 (2)	14 / 1391 (1)	7 / 653 (1)	2 / 420 (1)
Median Positive End-Expiratory Pressure (PEEP), cmH ₂ O	5.3 ± 1.8	5.6 ± 1.9	5.1 ± 1.7	5.1 ± 1.6	5.2 ± 1.7
Median Tidal Volume, mL	471 ± 131	461 ± 126	480 ± 135	462 ± 127	496 ± 139

Characteristic	Overall, N = 6657 ¹	Vasopressors discontinued for more than 24 hours at the time of weaning, N = 2745 ¹	Vasopressors discontinued for 24 hours or less at the time of weaning, N = 2257 ¹	Vasopressors at a dose of 5 µg/min or less at the time of weaning, N = 1036 ¹	Vasopressors at a dose greater than 5 µg/min at the time of weaning, N = 619 ¹
Median Respiratory Rate, breaths/min	18.7 ± 5.2	19.6 ± 5.2	17.9 ± 5.1	18.3 ± 5.3	18/1 ± 5
Median Fraction of Inspired Oxygen (FiO ₂)	40 ± 7	40 ± 7	41 ± 8	40 ± 7	40 ± 7
Median Last Recorded Rapid Shallow Breathing Index (RSBI) breath/min/L	47 ± 21	49 ± 21	45 ± 20	46 ± 21	45 ± 21
Median Richmond Agitation-Sedation Scale (RASS) Score	-1 ± 1	-1 ± 1	-1 ± 1	-1 ± 1	-1 ± 1
Arterial blood gases during weaning phase					
Median Lactate, mmol/L	1.7 ± 0.95	1.46 ± 0.74	1.76 ± 0.99	1.89 ± 0.96	2.03 ± 1.19
Median Arterial Blood pH	7.40 ± 0.06	7.41 ± 0.06	7.39 ± 0.06	7.39 ± 0.05	7.37 ± 0.05
Median Partial Pressure of Oxygen (PaO ₂), mmHg	126 ± 46	114 ± 35	131 ± 50	137 ± 55	131 ± 48
Median Partial Pressure of Carbon Dioxide (PaCO ₂), mmHg	41 ± 7	42 ± 8	40 ± 7	40 ± 6	40 ± 7

¹Mean ± SD; n / N (%)

Table 2. Secondary outcomes adjusted through inverse probability of treatment weighting

Adjusted secondary outcomes	Vasopressors discontinued for more than 24 hours at the time of weaning, N = 2745¹	Vasopressors discontinued for 24 hours or less at the time of weaning, N = 2257¹	Vasopressors at a dose of 5 µg/min or less at the time of weaning, N = 1036¹	Vasopressors at a dose greater than 5 µg/min at the time of weaning, N = 619¹
Day 30 mortality	13.4 (12.2-14.6)	14.5 (13.4-15.7)	13.1 (12-14.3)	12 (10.8-13.3)
In hospital mortality	11.7 (10.6-12.9)	13 (12-14.1)	11.7 (10.7-12.9)	10.5 (9.4-11.8)
Length of ICU stay, days	4.9 (4.7-5.2)	5.4 (5.1-5.7)	5.2 (4.9-5.4)	5 (4.7-5.3)
Length of hospital stay, days	13.5 (13.0-14.1)	14.7 (14.1-15.4)	14.4 (13.7-15.2)	14 (13.3-14.8)
Duration of post weaning mechanical ventilation, days	1.1 (0.9-1.2)	1.4 (1.3-1.6)	1.4 (1.2-1.5)	1.3 (1.2 – 1.5)
Day 28 Post weaning ventilator-free days	18.4 (17.9-18.9)	18.3 (17.8-18.7)	18.8 (18.3-19.3)	19.2 (18.7-19.7)

¹Mean ± SD; n / N (%) (95% (95%CI)

Assessing Safety of Mechanical Ventilation Weaning in Patients Receiving Continuous Vasopressors: An Emulated Target Trial

Authors: TBD

SUPPLEMENTAL MATERIAL

E-Figure 1: Definition of the initial and weaning phases of mechanical ventilation.

E-Figure 2: Directed Acyclic Graph (DAG) of the confounder model

E-Figure 3: Overlap assumption and density of propensity scores

E-Figure 4: Love plot of covariates balance for selected covariates

E-Figure 5: Average Treatment Effect (ATE) according to terciles of the Conditional Average Treatment Effect (CATE)

E-Figure 6: Risk differences as estimated by several causal inference methods compared to baseline (delayed strategy) for early, low-dose and high-dose strategy

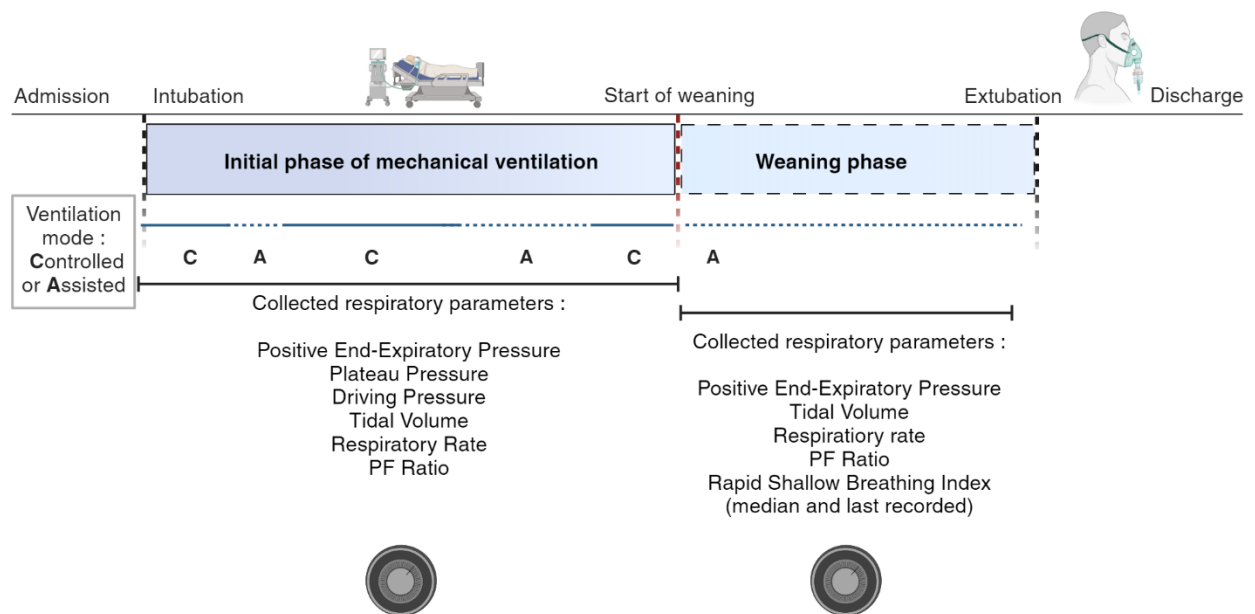
E-Table 1: Target trial and emulated trial components

E-Table 2: Extract from the BIDMC Weaning Protocol Guidelines

E-Figure 1: Definition of the initial and weaning phases of mechanical ventilation.

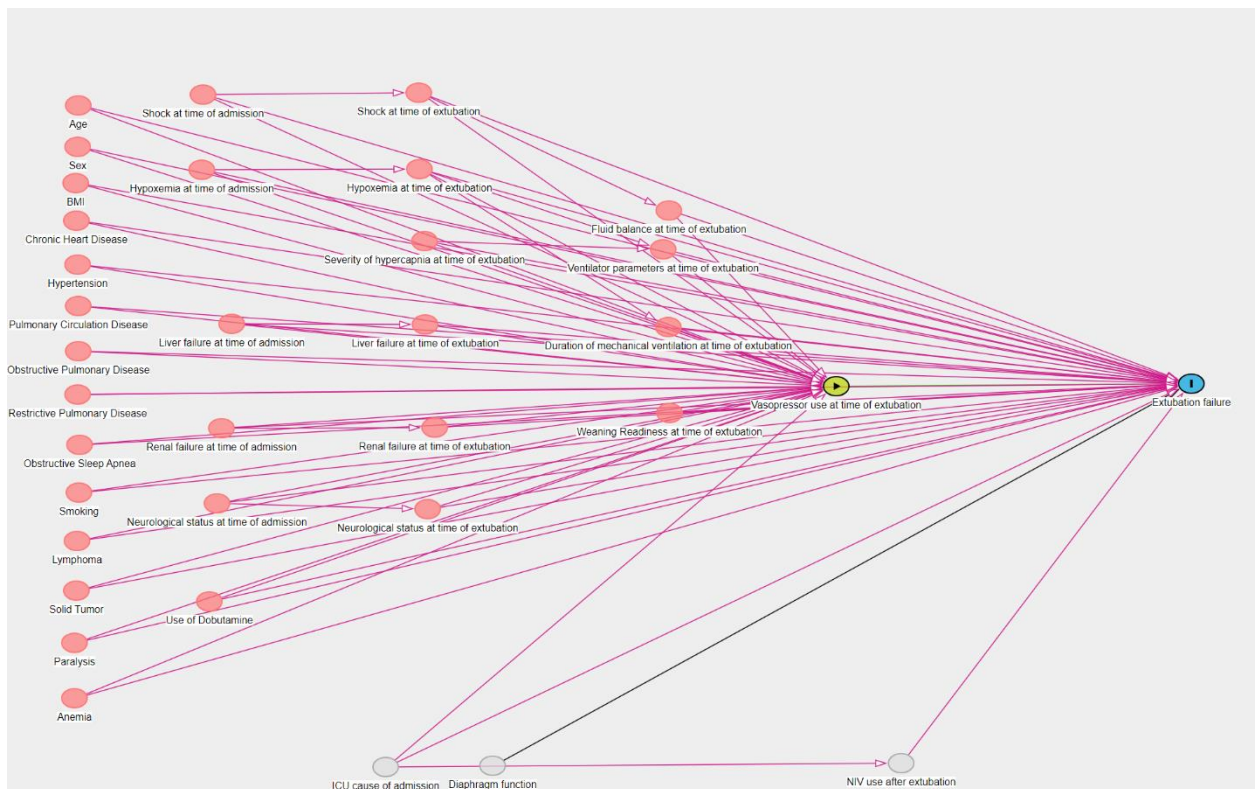
Each mode of ventilation was assessed and categorized into a controlled mode of ventilation or an assisted mode of ventilation according to the type of ventilation.

The weaning phase of mechanical ventilation was characterized by the first period of continuous assisted ventilation ending with weaning. For each phase, respiratory parameters were collected, and the median value was computed for every patient. The median value and last value recorded were retrieved for the Rapid Shallow Breathing Index (RSBI).



E-Figure 2: Directed cyclic graph (DAG) of the confounder model. (Made with DAGitty V3.0)

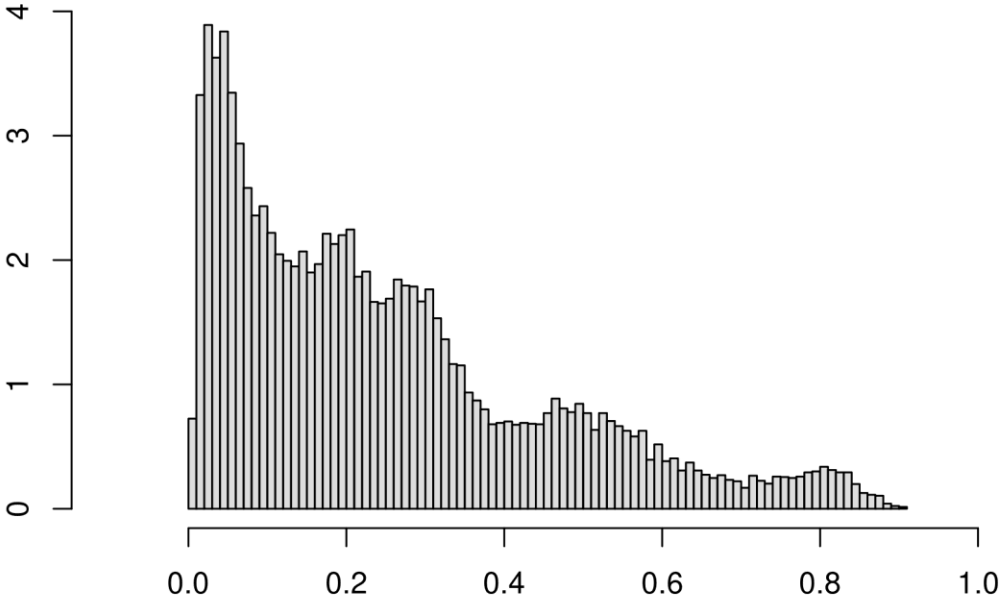
Blue is the outcome: weaning failure defined as reintubation by day 7 or death. Green is the exposure. Red are confounders variables, related to the exposure and the outcome and that should be controlled for in the analysis. Grey are unmeasured variables.



E-Figure 3: Overlap assumption and density of propensity scores

To estimate the treatment effect for a person with specific values for the set of covariates, we need to ensure that we are able to observe treated and untreated people with those same characteristics so that we can compare their outcomes. The overlap assumption states that at every point of the covariate space we can always find treated and control individuals. In other words, the probability of being treated, the propensity scores, should not be too close to zero or too close to one for the majority of patients. This is fundamental to estimate the causal effect of a treatment strategy, to have been observed in comparable settings, i.e., comparable values of covariates.

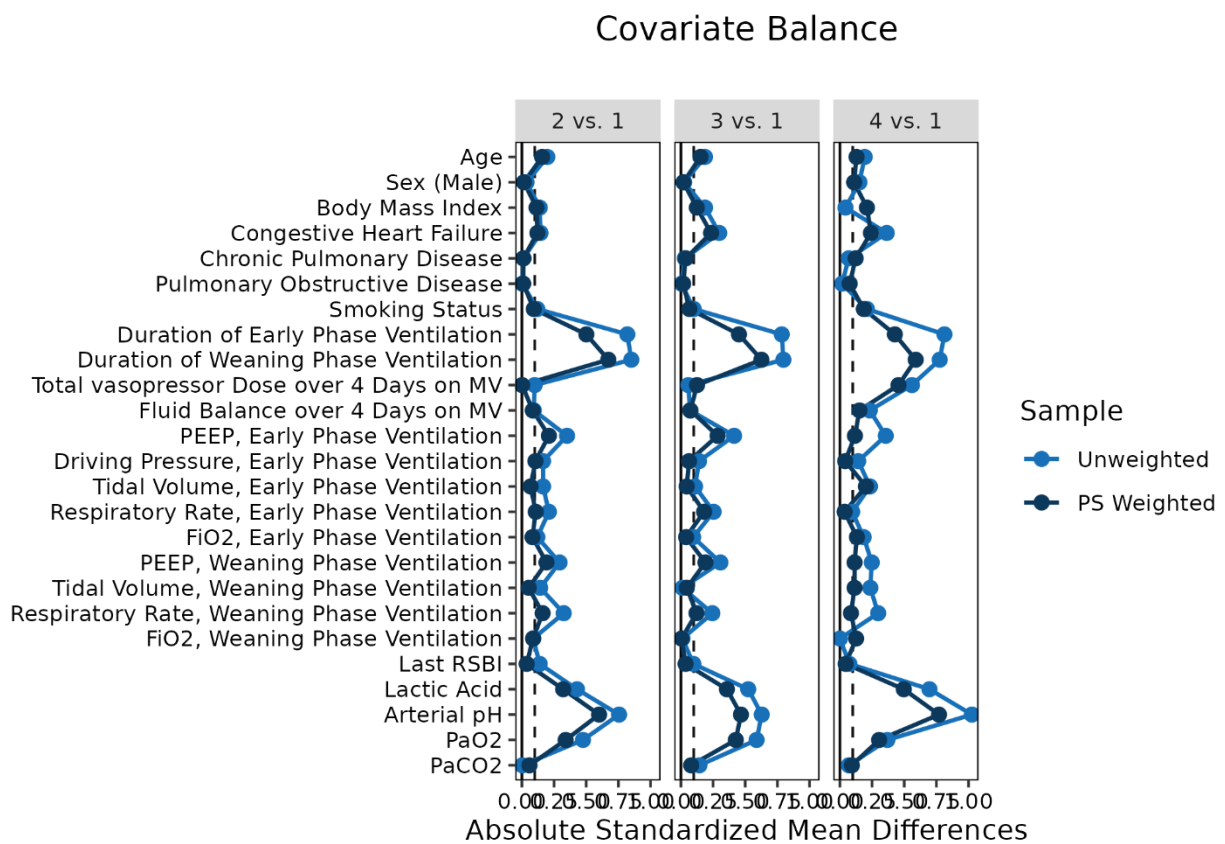
Estimated propensity scores (causal forest)



E-Figure 4: Love plot of covariates balance for selected covariates

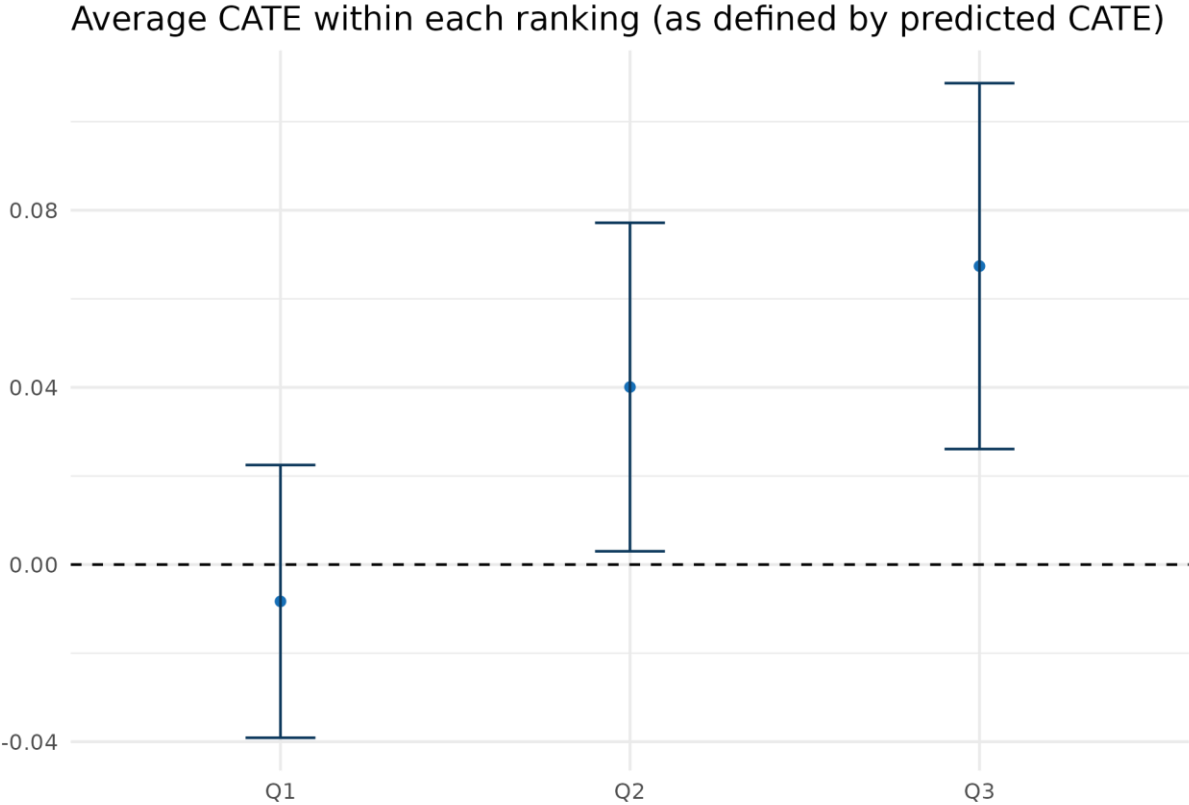
Absolute standardized mean differences for the main covariates of the confounder model are shown for the four studies strategies, before and after weighting with stabilized weights, computed as the inverse of the propensity score estimated through the causal forest model. A vertical dashed line represents a standardized mean difference of 0,10.

- 1: Delayed vasopressors discontinuation strategy (discontinuation for at least 24h before weaning)
- 2: Early vasopressors discontinuation strategy (discontinuation for 24h or less before weaning)
- 3: Low-dose vasopressors strategy (patients receiving vasopressors at a dose less than 5µg/min at the time of weaning)
- 4: High-dose vasopressors strategy (patients receiving vasopressors at least a dose of 5µg/min at the time of weaning)



E-Figure 5: Average Treatment Effect (ATE) according to terciles of the Conditional Average Treatment Effect (CATE)

To assess heterogeneity across subgroups, we split the data into groups based on terciles of the predicted treatment effect. We then compute the average treatment effect through averaging double robust scores to obtain the Augmented Inverse Propensity Weighted (AIPW) Average Treatment Effect. Asymptotically, the average estimates of the treatment effect should be monotonic for a large enough sample size.



E-Figure 6: Risk differences as estimated by several causal inference methods compared to baseline (delayed strategy) for early, low-dose and high-dose strategy

As a sensitivity analysis, several methods of confounding adjustment were used in this emulated trial to estimate the average causal effect of treatment in terms of risk differences.

First, we used inverse probability weighting to create a pseudo-population by weighting each individual using the inverse of the conditional probability of receiving the treatment strategy that they actually received.

By computing the difference in IP weighted averages of the outcomes in the treated and untreated populations, we can consistently estimate the average causal effect.

This allowed us to adjust for confounding factors by balancing the covariates between the treated and untreated populations. [1]

We used entropy balancing [2] to achieve a good balance for each treatment strategy, as this allowed us to adjust the different moments of the covariate distribution in each group: mean, standard deviation, and skewness.

The next step in estimating the average causal effect was to use the g-formula [3] to avoid a biased estimate built only on the treatment assignment model.

This involves specifying a model for the outcome as a function of treatment, covariates, and previously calculated weights. Then, for each individual, we compute their predicted values of the outcome setting their treatment status to treated, and then again for control, leaving us with two predicted outcome values for each unit, which are estimates of the potential outcomes under each treatment level. [4] The difference between the average of each prediction in each population, treated and untreated, is the estimate of the treatment effect, shown here as a causal risk difference.

Several models were compared for the outcome model: a logistic regression model, with and without interaction between the treatment and the covariates.

The pitfalls of this IPW and G-formula approach are the high variance of the estimates and possible model misspecification that can lead to a biased estimate. New methods were developed to address these concerns, as proposed by Robins et al [5] with augmented IPW or doubly robust methods.

The doubly robust methods, by considering a model for the treatment assignment and the outcome, dispose of better statistical characteristics, and are proven to be robust to either a treatment assignment model misspecification or to an outcome model misspecification.

Doubly robust methods are also more flexible from a modelling point of view, as they allow the use of modern machine learning methods that are able to capture non-linear relationships in the data.

Finally, we used the Augmented Inverse Propensity Weighted (AIPW) estimator through estimates of the causal forest model, with and without imputation of the dataset. To assess the robustness of the weights generated through the inverse of the propensity score, we used the causal forest model with the entropy balancing weights.

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3. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical Modelling.* 1986;7:1393-512.
4. Snowden JM, Rose S, Mortimer KM. Implementation of G-Computation on a Simulated Data Set: Demonstration of a Causal Inference Technique. *Am J Epidemiol.* 2011;173:731-8.
5. Robins JM, Rotnitzky A, Zhao LP. Analysis of Semiparametric Regression Models for Repeated Outcomes in the Presence of Missing Data. *Journal of the American Statistical Association.* 1995;90:106-21.

Abbreviations list

DR-GLM: Double Robust Method with Generalized Linear Model (Logistic Regression)

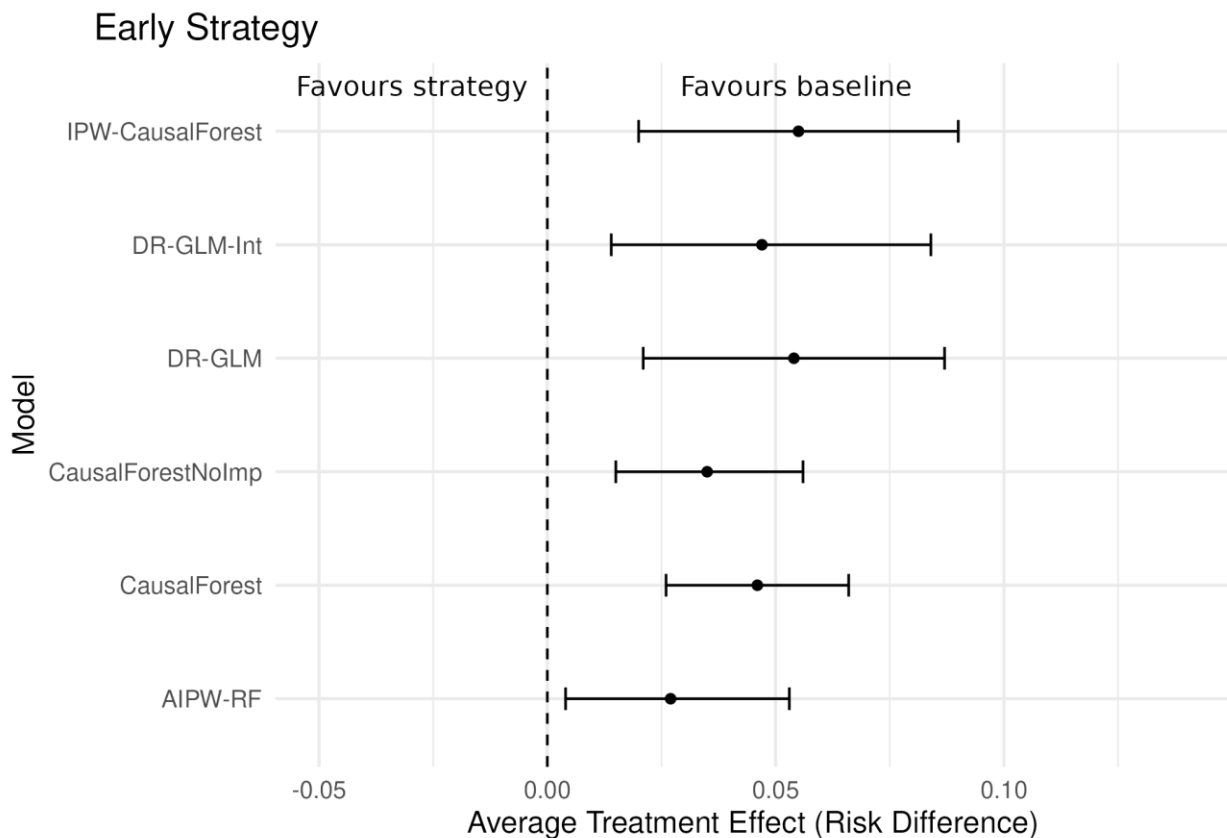
DR-GLM-Int: Double Robust Method with Generalized Linear Model (Logistic Regression)

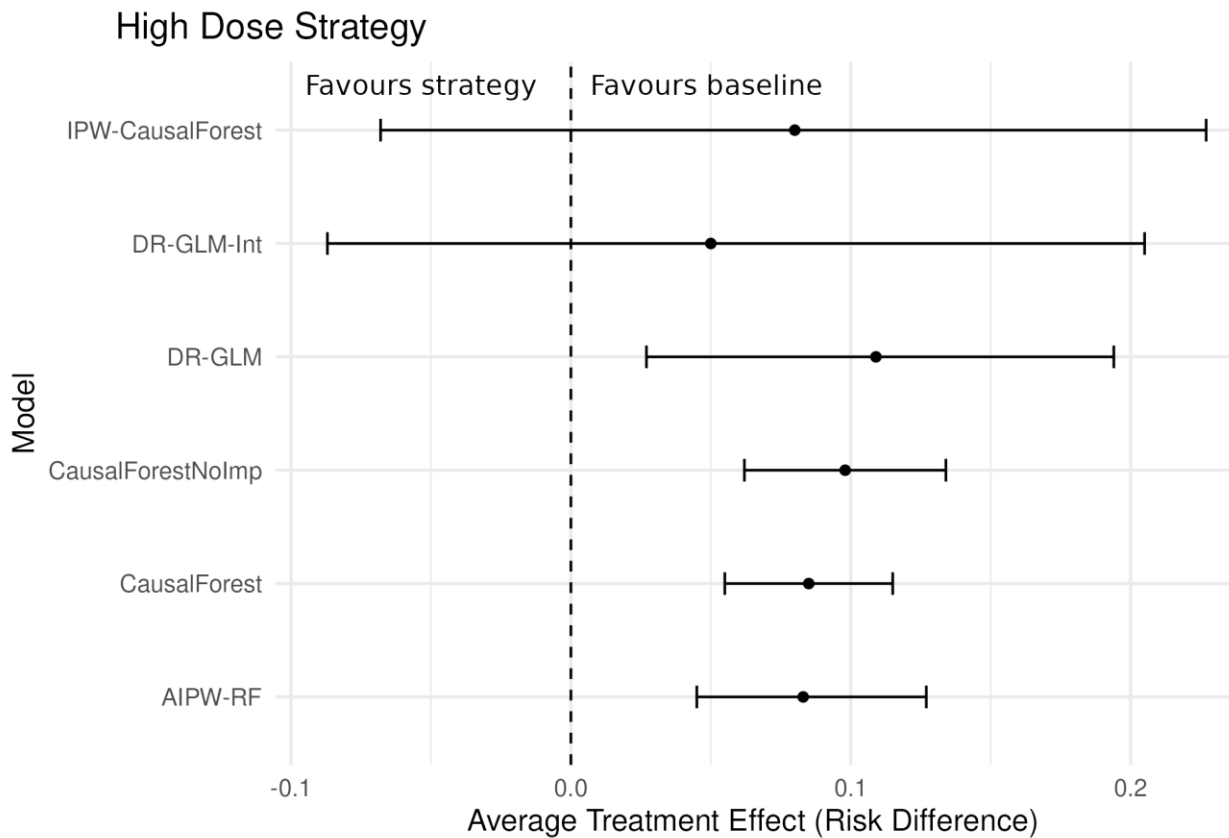
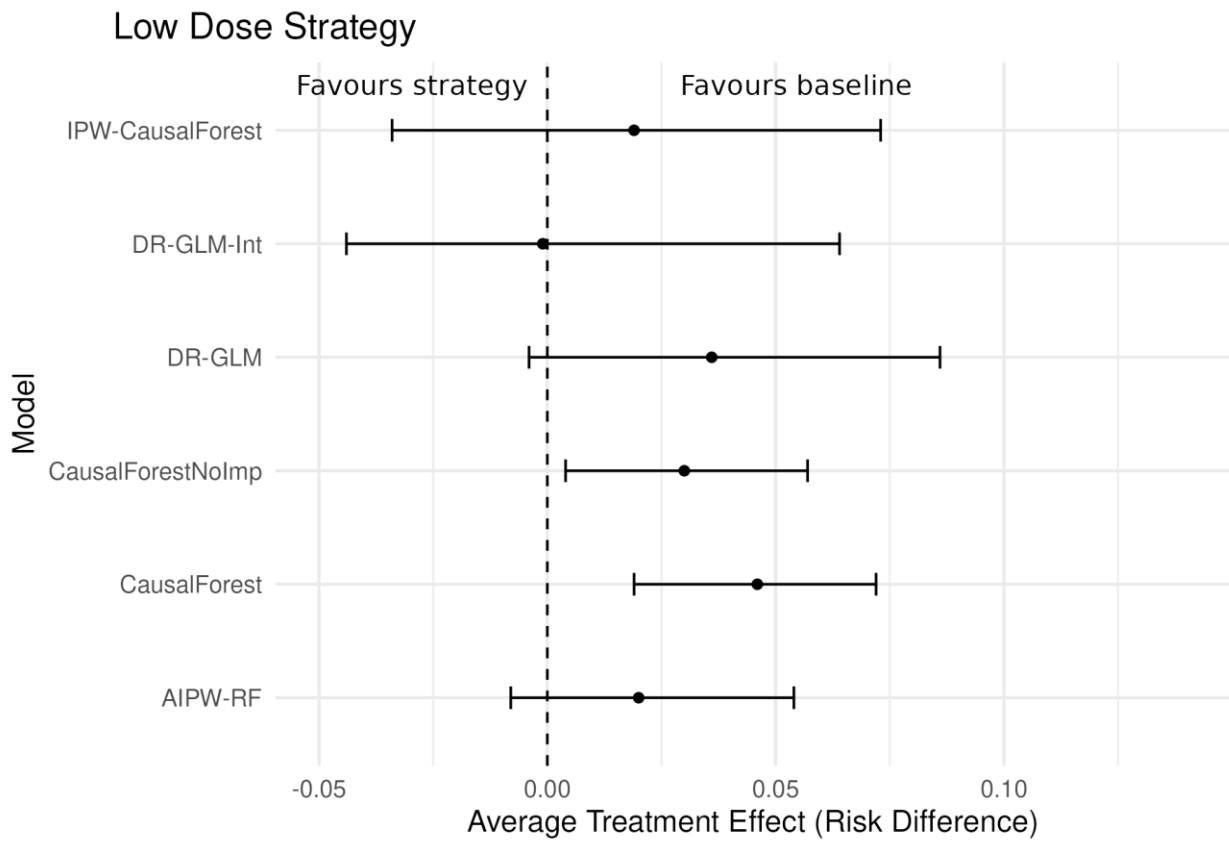
AIPW-RF: Augmented Inverse Propensity Weighted – Random Forest (For treatment and outcome models)

CausalForest: Causal Forest model and AIPW estimator with FAMD imputation

CausalForestNoImp: Causal Forest model without imputation of the dataset

IPW-CausalForest: Causal Forest model with entropy balancing weights for the treatment model





ETable 1: Target trial and emulated trial components

Protocol component	Target Trial Specification	Target Trial Emulation
Eligibility criteria	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> - Adult patients admitted to ICU, mechanically ventilated during their stay for more than 12 hours and receiving vasopressors at any point during mechanical ventilation <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> - DNI/DNR/CMO code status at any point during ICU stay - Surgery occurred a week before or a week after ICU intubation - Death occurred the same day as weaning 	Same as for the target trial
Treatment Strategies	<ol style="list-style-type: none"> 1. Weaning at any time if patients have been weaned from vasopressors for more than 24 hours. 2. Weaning at any time if patients have been weaned from vasopressors for 24 hours or less. 3. Weaning at any time while patients are receiving a vasopressor dose of 5 µg/min or less. 4. Weaning at any time while patients are receiving a vasopressor dose greater than 5 µg/min. 	Same as for the target trial
Assignment	Participants are randomly assigned to a strategy and physicians are aware of their assigned strategy.	We assume randomization conditional on the pre-specified baseline covariates adjustment via double robust methods
Follow-up	For each eligible individual, follow-up begins at assignment (weaning time) and continues until development of the outcome of interest (including death), discharge from hospital, or end of study at 7 days, whichever occurs first.	Same as for the target trial
Outcome	Reintubation or death in the 7 days following weaning	Same as for the target trial
Causal contrasts	Intention-to-treat effect Per-protocol effect	Observational analogue of the per-protocol effect
Data analysis	Intention-to-treat analysis Per-protocol analysis	Same as for the target trial per-protocol analysis We use Augmented Inverse Propensity Weighting (AIPW) to estimate the average treatment effect.

DNI: Do Not Intubate, DNR: Do Not Resuscitate, CMO: Comfort Measure Only

E-Table 2: Extract from BIDMC Weaning Protocol Guidelines

The use of sedatives and vasopressors does not specifically contraindicate weaning attempts.

If the patient meets the above criteria, a spontaneous breathing trial (SBT) is performed.

All failed and deferred SBTs should be re-screened and repeated later in the day.

The SBT should be continued for a maximum of 30 min unless ordered otherwise.

Criteria needed to enter the weaning protocol	Criteria needed prior to weaning
PEEP less than or equal to 10 cmH ₂ O	Successful completion of SBT
SpO ₂ greater than 90% at FiO ₂ less than 0.60	Effective clearance of secretions
pH greater than or equal to 7.35	Adequate airway protection
No active ectopy/ischemic changes have occurred.	Confirmed with MD and POE order in place

MD: Medical Doctor. POE: Physician's Order Entry.

SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*
- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*
- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*
- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*
- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

RESUME

Introduction :

Le sevrage de la ventilation mécanique des patients est un moment clé du séjour en réanimation. Dans une population mixte de patients médicaux et chirurgicaux, une étude rétrospective a montré que l'extubation avec une faible dose de vasopresseurs (définie comme une dose inférieure à 0.1 µg/kg/min) était associée à une mortalité diminuée et à une durée de séjour en service de réanimation plus courte en comparaison avec des patients extubés hors traitement vasopresseur. Nous avons réalisé un essai clinique émulé visant à comparer quatre stratégies de sevrage des vasopresseurs chez des patients médicaux adultes admis en réanimation et bénéficiant d'un sevrage de la ventilation mécanique. Notre hypothèse principale était que la stratégie de sevrage de la ventilation mécanique avec une faible dose de vasopresseurs dans une population de patients médicaux était à plus faible risque d'échec d'extubation.

Méthodes : Nous avons réalisé un essai émulé avec des données de patients admis dans les unités de réanimation du Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA de Janvier 2011 à Juin 2022. Nous avons comparé quatre stratégies d'arrêt des vasopresseurs pendant le sevrage de la ventilation mécanique : sevrage tardif (vasopresseurs arrêtés depuis 24 heures ou plus au moment de l'extubation), sevrage précoce (vasopresseurs arrêtés depuis moins de 24 heures au moment de l'extubation), sevrage avec faible dose de vasopresseurs (à une dose de 5 µg/min ou moins), et sevrage avec forte dose de vasopresseurs (à une dose supérieure à 5 µg/min). L'échec d'extubation était défini comme le décès ou la réintubation avant le 7^{ème} jour post extubation et constituait le critère de jugement principal.

Résultats :

La stratégie de sevrage précoce générait un nombre de cas excédentaires d'échec d'extubation de 35 (IC95%, 14,8 à 55) pour 1000 patients (Différence de Risque (DR) = 0,035, IC à 95%, 0,0148 à 0,055), comparativement à la stratégie de sevrage tardive. Pour la stratégie d'extubation avec une faible dose de vasopresseurs, les cas excédentaires d'échec d'extubation étaient estimés à 30 (IC à 95%, 4 à 56) pour 1000 patients (DR = 0,030, IC95%, 0,004 à 0,056). Le nombre de cas excédentaires estimés le plus élevé d'échec d'extubation se trouvait dans la stratégie d'extubation avec haute dose de vasopresseur, avec un nombre de cas excédentaires estimé à 95 (IC95%, 60 à 130) pour 1000 patients (RD = 0,095, IC95%, 0,060 à 0,130).

Conclusion : Cet essai émulé montre que la stratégie la plus sûre pour limiter le décès ou la réintubation à J7 est d'attendre au moins 24h après l'arrêt du vasopresseur pour procéder à l'extubation. Dans une population de patients médicaux, la stratégie de sevrage de la ventilation mécanique avec une faible dose de vasopresseurs a montré un modeste surrisque d'échec d'extubation, mais est associé à une durée globale plus courte de ventilation mécanique. Cet essai émulé pourrait guider la conception de futurs essais randomisés, lesquels pourraient évaluer la réduction potentielle de la durée de la ventilation mécanique grâce à la stratégie de sevrage de la ventilation mécanique avec une faible dose de vasopresseurs.

SPECIALITE : Médecine intensive-réanimation

MOTS-CLÉS

Inférence causale, Ventilation mécanique, Sevrage, Vasopresseurs, Essai ciblé émulé