



The Effect on Extubation of Early vs. Late Definitive Closure of the Patent Ductus Arteriosus in Premature Infants: A Target Trial Emulation Using Electronic Health Records and A Target Trial Emulation Comparing High-frequency Jet Ventilation Management Strategies for Respiratory Acidosis among Neonates with Respiratory Failure

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**The Effect on Extubation of Early vs. Late Definitive Closure of the
Patent Ductus Arteriosus in Premature Infants: A Target Trial
Emulation Using Electronic Health Records**

and

**A Target Trial Emulation Comparing High-frequency Jet Ventilation
Management Strategies for Respiratory Acidosis among Neonates
with Respiratory Failure**

by

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A Dissertation Submitted to the Faculty of Harvard Medical School in Partial
Fulfillment of the Requirements for the Degree of Master of Medical Sciences in
Clinical Investigation (MMSCI)

May 24, 2025

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Overview

It's well established that the key advantages of a randomized trial include: marginal exchangeability between groups, clear specification of time zero, and synchronization of eligibility check and treatment assignment with time zero. These features become even more apparent when considering the challenges of drawing causal conclusions from observational data. A reliable approach to maintaining the key attributes of randomized trials in observational analyses is to design them in a way that explicitly emulate a hypothetical randomized trial aimed at answering the causal research question — the *target trial*.

Premature infants are often referred for the definitive procedural closure of the patent ductus arteriosus (PDA) with the failure of, or contraindication to, pharmacotherapy and the inability to wean respiratory support. However, once this need is identified, the importance of expedited closure is unclear. We first specified a hypothetical randomized trial (the "*target trial*") that would estimate the effect on extubation of early (0–4 days from referral) vs. late (5–14 days from referral) definitive PDA closure. We then emulated this target trial via inverse probability (IP) weighting, using a single-institution registry of premature infants (born <30 weeks or with a birth weight < 1500 g) who underwent the definitive closure of PDA between January 2014 and October 2023. The objective of this study was to compare the effect of the timing of definitive closure (i.e., surgical ligation or device occlusion) on early respiratory outcomes in premature infants without complex congenital cardiac disease.

High-frequency jet ventilation (HFJV) is often used in neonatal intensive care units (NICUs) to treat respiratory failure. In neonates initiating HFJV for hypercarbic respiratory failure, clinicians aim to adjust ventilator settings to achieve a gradual reduction in $p\text{CO}_2$. Rapid correction with a large shift in $p\text{CO}_2$ may lead to cerebrovascular spasm and increase the risk of neurovascular injury. However, specific management of HFJV peak inspiratory pressure (PIP) varies across institutions. Here, we use EHR data and aim to compare two dynamic PIP management strategies by emulating a pragmatic target trial. We illustrate the use of inverse probability (IP) weighting to adjust for time-varying confounding.

Project 1

Article (published version)

The Effect on Extubation of Early vs. Late Definitive Closure of the Patent Ductus Arteriosus in Premature Infants: A Target Trial Emulation Using Electronic Health Records

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Abstract: Background/Objectives: Premature infants are often referred for the definitive procedural closure of the patent ductus arteriosus (PDA) with the failure of, or contraindication to, pharmacotherapy and the inability to wean respiratory support. However, once this need is identified, the importance of expedited closure is unclear. The objective of this study was to compare the effect of the timing of definitive closure (i.e., surgical ligation or device occlusion) on early respiratory outcomes in premature infants. **Method:** We first specify a hypothetical randomized trial (the “target trial”) that would estimate the effect on extubation of early (0–4 days from referral) vs. late (5–14 days from referral) definitive PDA closure. We then emulate this target trial using a single-institution registry of premature infants (born <30 weeks or with a birth weight < 1500 g) who

underwent the definitive closure of PDA between January 2014 and October 2023. **Results:** We identify 131 eligible infants. At the end of the follow-up, 70 and 38 infants were adherent to early and late PDA closure strategies, respectively. The cumulative incidence of extubation in the early group was higher than that in the late group until day 40 (maximum risk difference: 22 percentage points at day 13; 95% CI: -11 to 56). Outcomes were similar at the end of the 45-day follow-up period (risk difference: -1 percentage point; 95% CI: -46 to 42). **Conclusions:** The need for mechanical ventilation was equivalent between early and late PDA closure strategies at the end of a 45-day follow-up period although infants in the early intervention group were extubated sooner.

Keywords: prematurity; patent ductus arteriosus; bronchopulmonary dysplasia; extubation success; target trial emulation; device closure; surgical ligation

1. Introduction

Premature infants with patent ductus arteriosus (PDA) causing cardiovascular compromise are often referred for definitive procedural closure when expectant management or pharmacotherapy fails, there is a contraindication to medications, or there remains an inability to wean mechanical ventilation. The decision to perform a definitive procedure via the surgical ligation or device occlusion of PDA is then balanced between the potential benefit of instantaneous closure and clinical improvement with the possibilities of peri-procedural instability and spontaneous improvement (1-5).

As the field continues to debate the need for PDA closure with uncertainty persisting around the "if" and "how" to treat, it remains critical to understand the impact that timing from referral (once the decision has been made to remove PDA with a definitive option) to the actual closure of PDA has on respiratory morbidity and other outcomes. PDA trials have often utilized short- and long-term respiratory morbidity as outcome measures because of the known associations of prolonged exposure of shunt volume with longer durations of mechanical ventilation and the development of bronchopulmonary dysplasia (BPD) (6-9). Several studies have previously reported on the optimal timing of definitive closure (1,2,4,10-12). However, important components of study design (such as heterogeneous eligibility criteria and vaguely defined interventions) and analysis (such as the unintentional creation of immortal time bias) deviate from the way in which a randomized control trial (RCT) would be implemented, limiting the interpretability of effect estimates. In addition, most studies examining the timing of definitive closure have focused on surgical ligation (1,2,4,10-12) while transcatheter device occlusion is now the prevailing approach for the definitive closure of PDA in premature infants (13,14).

Accordingly, the primary objective of this study was to compare the effect of time from referral to definitive closure on short-term respiratory outcomes in premature infants without complex congenital cardiac disease.

2. Materials and Methods

We first specify the hypothetical randomized trial (the “target trial”) we would want to perform to estimate the effect on extubation of early vs. late definitive PDA closure. We then emulate that trial using data from electronic health records. This two-step approach (i.e., first specifying and then emulating a target trial) mitigates common avoidable analytical errors in observational analyses.

2.1. Specification of the Target Trial

We describe a hypothetical randomized control trial enrolling premature infants at a single institution who were referred for definitive closure of PDA between January 2014 and October 2023 (**Table 1**).

2.1.1. Eligibility Criteria

Infants would be eligible to participate in this study if they were born before 30 weeks of gestational age or had birth weights of less than 1500 g. All eligible participants would have PDA considered to be hemodynamically significant by a treating clinician and would be mechanically ventilated at the time of referral. Eligible infants would have received at least one course of pharmacotherapy prior to referral unless contraindicated. Neonates would be excluded in the presence of complex congenital cardiac disease (defined as anomalies other than hemodynamically insignificant atrial septal defect, ventricular septal defect, or patent foramen ovale), bidirectional or right-to-left direction of PDA flow, major congenital anomalies, or a tracheostomy.

Table 1. Specification of the target trial and description of its emulation.

Protocol Component	Specification of the Target Trial	Target Trial Emulation
Eligibility criteria	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> - Born < 30 weeks gestational age or birth weight less than 1500 grams - Mechanically ventilated at referral - Have a diagnosis of PDA confirmed by echocardiography and referred for closure intervention 	Same as target trial
	<ul style="list-style-type: none"> - Failed, or have contraindications to, at least one pharmacologic therapy* <u>Exclusion criteria:</u> <ul style="list-style-type: none"> - Complex congenital cardiac disease - Bidirectional or R-L flow in PDA - Major congenital anomalies 	

Treatment strategies**	(1) Undergo “early” intervention for PDA closure within 0–4 days of randomization (2) Undergo “late” intervention for PDA closure within 5–14 days of randomization	(1) Undergo “early” intervention for PDA closure within 0–4 days of referral (2) Undergo “late” intervention for PDA closure within 5–14 days of referral
Treatment assignment	Random assignment to a treatment arm without blinding	Each individual is classified into both strategies at baseline
Primary outcome	Extubation	Same as target trial
Follow-up period	Follow-up begins at the time of assignment and ends at 45 days or at death, whichever occurs first	Same as target trial
Causal contrast	Per-protocol effect	Observational analog of per-protocol effect Same as target trial with the following modification: Since treatment assignment is unknown, eligible individuals contribute clones to each treatment arm. A given clone is censored at the time of deviation from the assigned treatment strategy
Analysis plan	Per-protocol analysis: censoring individuals if/when they do not adhere to their treatment assignment, with inverse probability of treatment weighting to adjust for selection bias	

* Including indomethacin, ibuprofen, and/or acetaminophen. ** In the target trial specification, the specific day of intervention within the assigned range (grace period) is left to the treating physician’s discretion and logistical factors; in the target trial emulation, the analytical choice is made to specify that neonates undergo interventions in a uniform distribution within the assigned range.

2.1.2. Treatment Strategies

Eligible participants would be assigned to undergo PDA closure within 0–4 days of randomization (“early” intervention) or between 5 and 14 days after randomization (“late” intervention). For either strategy, the determination of timing of intervention would be left to the treating physician’s discretion and logistical factors (e.g., surgeon or interventionalist availability, transport requirements, distance from high-volume center, healthcare insurance clearance, etc.). We refer to the number of days after which the specified intervention strategy may take place as a “grace period.”

2.1.3. Treatment Assignment

Treatment would be assigned randomly in a non-blinded fashion.

2.1.4. Outcome

The primary outcome of interest is successful extubation, defined as lack of invasive mechanical ventilation for at least seven days after extubation (15).

2.1.5. Follow-Up

Beginning at the time of referral (time zero and randomization), the primary outcome would be assessed over a 45-day follow-up period. The time of referral would coincide with the times of eligibility assessment and treatment assignment.

2.1.6. Casual Contrast

In the target trial, it would be straightforward to estimate the intent-to-treat effect or the effect of assignment to early or late intervention (regardless of adherence to this assignment). However, we would also estimate a non-naive per-protocol effect (specifically, the effect of adhering to the assigned treatment with complete follow-up), which may be of greater clinical interest.

2.1.7. Analysis

To estimate this per-protocol effect using data from the target trial, we would fit a treatment model over the grace period for each intervention among all eligible individuals who had not deviated from their assigned treatment arm. This model could be adjusted for baseline and possibly post-baseline prognostic factors that predicted adherence. In this case, the adjustment set would include baseline covariates of birth weight, gestational age, age at referral, sex, year of enrollment, and prior attempt(s) of pharmacological treatments for PDA (**Table S1**). Of note, neonates who die prior to the study endpoint would be considered to be intubated until the end of the follow-up period, corresponding to a total effect type of estimand. (Estimation of an alternative estimand, the controlled direct effect, is described below in a sensitivity analysis.) We would then estimate inverse probability of treatment weights from this model and, subsequently, fit a weighted pooled logistic regression model to estimate the cumulative incidence of extubation over the follow-up period.

We could additionally perform three sensitivity analyses. First, the controlled direct effect (as compared with the total effect of the main analysis) could be estimated in the absence of competing risk events (e.g., had no participants died). Second, the main analysis could be repeated with the inclusion of referral site in the confounder set. Third, the estimated cumulative incidence of extubation could be compared between a strategy of intervention for PDA at a younger age (e.g., PDA closure between 15 and 20 days) and one at an older age (e.g., PDA closure between 21 and 35 days) among neonates referred for intervention before 14 days of age.

2.2. *Emulation of the Target Trial*

This study was approved by the Boston Children's Hospital Institutional Review Board (IRB-P00035857). In 2019, we established a quality-improvement-based registry of all infants referred to Boston Children's Hospital for consideration of definitive closure. We analyzed data from infants with PDA referred to a quaternary care center for surgical ligation or transcatheter closure. Infants' demographic, clinical, echocardiographic, and procedural data had been entered into the registry. The date of referral for consideration of definitive closure had also been documented.

The eligibility criteria, treatment strategies, follow-up, and outcome were the same as those specified in the target trial above. We note the following differences in the target trial emulation.

2.2.1. Treatment Assignment

Each eligible participant is classified into both strategies at baseline.

2.2.2. Causal Contrast

The casual contrast is an observational analog of the per-protocol effect.

2.2.3. Analysis

The analysis of the per-protocol effect would follow that of the target trial with the following exception. In the observed data, baseline labels of treatment assignment do not exist, and an individual's data may be compatible with both treatment arms at a given time. That is, during the early grace period (days 0–4), a participant's observed data may, at times, be consistent with both strategies. One analytical option would be to flip a fair coin for each individual and thereby randomly assign the treatment arms. Instead, for statistical efficiency, we create two clones of each individual and assign one clone to each of the two treatment strategies. Each eligible patient contributes one clone to each treatment arm so long as they remain compatible with that strategy. A clone would then be censored for deviation from the assigned treatment strategy at the time of deviation. The code for the analysis (R version 4.4.2) is available on GitHub (<https://github.com/zhou996996/PDA-timing-study/tree/main> (accessed on 13 March 2025)).

3. Results

In the emulation of the target trial, a total of 131 neonates met the eligibility criteria between 1 January 2014 and 31 October 2023. At the end of the follow-up, 70 and 38 neonates had histories consistent with the early and late PDA closure strategies, respectively. One neonate followed both strategies due to early extubation without intervention; 24 neonates initially followed one or both strategies but ultimately deviated from both strategies. **Figure 1** displays a flowchart of the study population.

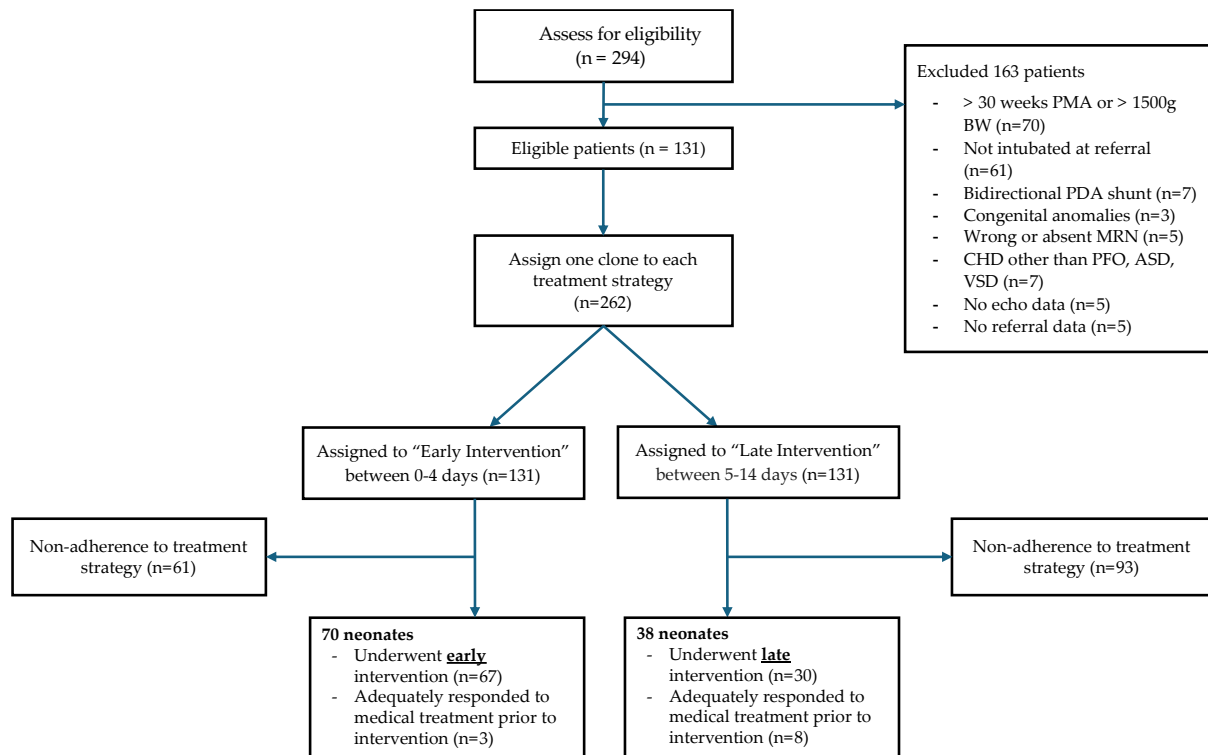


Figure 1. Study flowchart

The median gestational ages (24.5 weeks vs. 24.5 weeks) and birth weights (745 g vs 732.5 g) were similar in the early and late groups. Over 90% of neonates had PDA only for both groups (**Table 2**). After adjustment, characteristics were generally similar between the groups, except that neonates in the early intervention group were more frequently white (52% vs. 41%) compared with those in the late intervention group. During the last assessment before PDA intervention, the diameters of the duct (2.5 mm vs. 2.4 mm) were also similar in the early and the late groups (**Table S2**).

Table 2. Characteristics of eligible individuals referred for intervention for PDA closure (2014–2023) at the end of the grace period.

	Early Group <i>n</i> = 70 Unweighted	Late Group <i>n</i> = 38 Unweighted	Early Group <i>n</i> = 166 Weighted	Late Group <i>n</i> = 94 Weighted
GA at birth, wks	25 [24, 25]	25 [2, 24]	24 [23, 25]	24 [24, 25]
PMA at referral, wks	28 [27, 28]	27 [25, 28]	27 [25, 28]	27 [27, 28]
Age at referral, days	19 [13, 24]	13 [6, 21]	15 [11, 23]	20 [13, 26]
Birth weight, g	745 [633, 859]	733 [593, 870]	680 [550, 852]	736 [604, 849]
Female (%)	28 (40.0)	22 (57.9)	78 (46.7)	38 (40.3)
Year of referral	2018 [2015, 2020]	2021 [2016, 2022]	2019 [2015, 2022]	2017 [2015, 2020]
APGAR1 *	3.0 [1.0, 5.0]	3.0 [1.0, 6.0]	4.0 [2.0, 5.0]	3.0 [1.0, 5.0]
APGAR5 *	6.5 [5.0, 8.0]	6.0 [5.5, 8.0]	7.0 [5.0, 7.0]	6.0 [5.0, 8.0]
Race (%)				
White	27 (38.6)	13 (34.2)	86 (51.9)	39 (41.4)
Black	16 (22.9)	12 (31.6)	28 (17.1)	20 (21.7)
Asian	2 (2.9)	3 (7.9)	3 (1.9)	4 (4.0)

Other/Unknown	25 (35.7)	10(26.3)	48 (29.1)	31 (32.0)
Surfactant use (%)	67 (95.7)	33 (86.8)	161 (96.8)	88 (93.8)
Inotropes use *	11 (19.0)	10 (43.5)	28 (26.3)	19 (24.3)
PDA medications **	61 (87.1)	28 (73.7)	133 (80.1)	81 (86.3)
CHD type				
Only PDA	65 (92.9)	36 (94.7)	159 (96)	88 (93.3)
PDA and ASD	4 (5.7)	1 (2.6)	5 (3)	5 (5)
PDA and VSD	1 (1.4)	1 (2.6)	2 (1)	2 (1.7)

Data are presented as median (interquartile range) or number (percent); *ASD*: atrial septal defect; *CHD*: congenital heart disease; *GA*: gestational age; *PMA*: postmenstrual age; *PDA*: patent ductus arteriosus; *VSD*: ventricular septal defect. * Missing data: APGAR ($n = 5$, 4%) and inotrope use ($n = 34$, 26%). ** PDA treatment courses were missing for 15 neonates (12%), who were counted as not having had PDA treatment.

The estimated cumulative incidence of extubation at day 14 from referral was higher in the early group (38%; 95% CI: 10 to 72%) than in the late group (16%; 95% CI: 6 to 39%) with a cumulative incidence difference of 22 percentage points (95% CI: -11 to 56). At the end of the 45-day follow-up period, the estimated cumulative incidence values of extubation were similar between the groups (64%; 95% CI: 38 to 87% in the early group and 65%; 95% CI: 28 to 98% in the late group) with a cumulative incidence difference of -1 percentage point (95% CI: -46 to 42). Neonates in the early intervention group were extubated sooner than those in the late intervention group until day 35. The maximum cumulative incidence difference occurred at day 13 (21 percentage points, 95% CI: -11 to 55) with cumulative incidence values of extubation of 36% (95% CI: 10 to 71%) in the early group and 15% (95% CI: 5 to 38%) in the late group. The cumulative incidence of extubation over the 45-day follow-up period and cumulative incidence differences are illustrated in **Figure 2** and **Table 3**. The estimated mean ventilator days were lower in the early group than in the late group throughout the study. At the end of follow-up period, they were 26.3 days (95% CI: 14.8 to 37.4) and 30.8 days (95% CI: 19.3 to 39.4) in the early and late group, respectively, with a difference of -4.5 days (95% CI: -18.5 to 11.5).

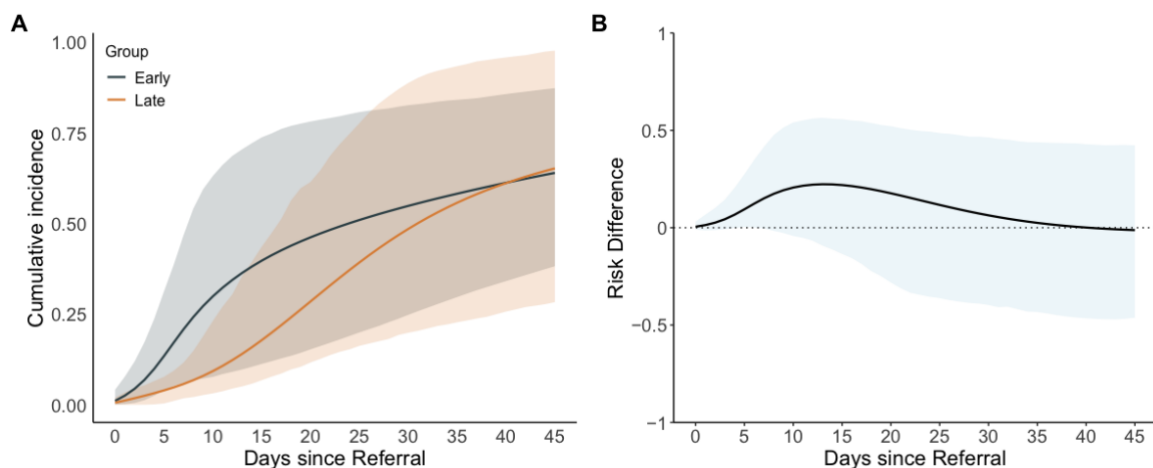


Figure 2. Estimated cumulative incidence and cumulative incidence differences in extubation since referral for patent ductus arteriosus intervention, comparing early

(0–4 days from referral) with late (5–14 days from referral) interventions. **(A)** Estimated cumulative incidence (95% confidence interval shaded); **(B)** estimated cumulative incidence difference (95% confidence interval shaded) using the late group as the reference.

Table 3. Estimated cumulative incidence of extubation and differences at selected time points.

	Day 7	Day 14	Day 30	Day 45
Early PDA intervention (%)	21 (6, 47)	38 (10, 72)	55 (25, 83)	64 (38, 87)
Late PDA intervention (%)	6 (2, 12)	16 (6, 39)	49 (20, 89)	65 (28, 98)
Difference (ref. late) (%)	15 (0, 41)	22 (-11, 56)	6 (-40, 46)	-1 (-46, 42)

PDA: patent ductus arteriosus.

Events and outcomes at the end of the grace period are summarized in **Table S3**. The results favored earlier repair in a sensitivity analysis comparing intervention at a younger age (15 to 20 days) with intervention at an older age (21 to 35 days) among neonates referred for intervention before 14 days of age (**Figure 3** and **Table 4**).

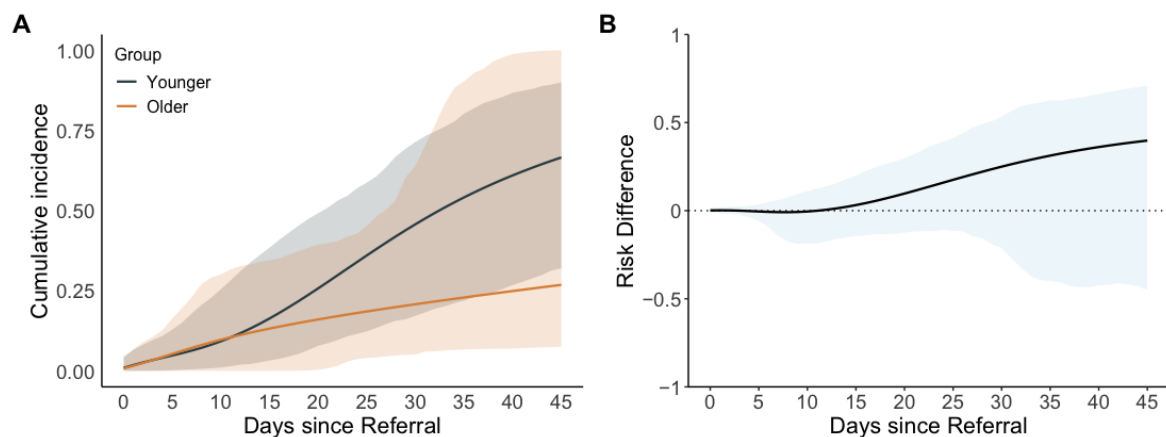


Figure 3. Estimated cumulative incidence and cumulative incidence difference comparing strategies of patent ductus arteriosus closure at a younger (15 to 20 days of life at intervention) vs. older age (21 to 35 days of life at intervention) for neonates referred before 14 days of age (sensitivity analysis #3). **(A)** Estimated cumulative incidence (95% confidence interval shaded); **(B)** estimated cumulative incidence difference (95% confidence interval shaded), using the older group as the reference.

Table 4. Estimated cumulative incidence of extubation and differences between a strategy of PDA closure at a younger (14 to 20 days of life at intervention) vs. one at an older age (21 to 35 days of life at intervention) at selected time points among neonates referred before 14 days of age (sensitivity analysis #3).

	Day 7	Day 14	Day 30	Day 45
Younger group (%)	6 (0, 18)	15 (3, 36)	46 (17, 71)	67 (32, 90)
Older group (%)	7 (0, 23)	13 (0, 34)	21 (5, 64)	27 (8, 100)
Difference (ref. older) (%)	-1 (-14, 6)	2 (-15, 18)	25 (-21, 53)	40 (-45, 71)

PDA: patent ductus arteriosus.

The results of the sensitivity analyses 1 and 2 are similar to those of the main analysis. Neonates in the early intervention group were extubated sooner than those in the late intervention group for most of the study period while the cumulative incidence was similar between groups at the end of the follow-up period. The results of sensitivity analysis 1 are presented in **Figure S1** and **Table S4**. Those of sensitivity analysis 2 are presented in **Figure S2** and **Table S4**.

4. Discussion

Our findings suggest that, among premature infants without complex congenital heart disease, earlier definitive PDA closure may be associated with earlier extubation compared with delayed intervention. Over a longer-term (45-day) follow-up, there was no difference in the extubation rates based on timing from referral to definitive closure, but those in the early closure group were exposed to fewer ventilator days. As such, these results support an urgency for the definitive closure of PDA.

Prior studies evaluating the timing of definitive PDA closure have deviated from study design principles in a number of ways that may introduce bias. First, the analyses have generally made oversimplified comparisons of outcomes based on the ages of neonates who underwent PDA closure (1–4,10,11). In doing so, eligibility criteria have been applied to the groups at different times, which may have introduced immortal time bias. For example, individuals in a late group must, implicitly, have survived and remained intubated, with symptomatic PDA, to be included in that group. Additionally, defining the treatment strategy using only age (e.g., <14 or <21 days after birth) without establishing a time of baseline (when eligibility would be assessed and follow-up would begin) does not consider when the PDA became symptomatic or the time of first eligibility. By introducing a grace period and including participants in as many treatment strategies as they are eligible for, the present study describes how to avoid this type of bias. When we applied this methodology to a strategy of PDA closure based on age in a sensitivity analysis, estimates were imprecise but favored a strategy of PDA closure at a younger age.

The optimal time to close hemodynamically significant PDA (hsPDA) has previously been explored in the context of “length of exposure” under the assumption that PDA causes cardiovascular compromise from birth until the date of closure (16–18). There is evidence suggesting that prolonged exposure to hsPDA impacts both short- and long-term respiratory morbidity (7,18), which is even more pronounced among neonates who remain mechanically ventilated for greater than 10 days (19). The timing from referral to definitive closure (a surrogate for the identification of the hemodynamic significance) may better reflect the actual length of exposure. Additionally, the results of these prior studies are difficult to interpret given that length of exposure is not in and of itself a well-defined clinical intervention (unlike a procedure to close PDA).

The impact of the timing of definitive PDA closure on clinical outcomes has generally been explored in studies of open surgical PDA ligation via thoracotomy. Until recently, the primary method for definitive closure of PDA was surgical ligation in premature infants < 2 kg. Following the United States Food and Drug

Administration approval of a transcatheter occlusive device in premature infants in 2019, our practice changed to offering this minimally invasive approach as a first-line option. The rapid adoption of transcatheter device occlusion as the primary definitive closure option in premature infants has pushed the field to consider its impact on outcomes separate from surgical ligation (14). Earlier referral and subsequent prompt closure for premature infants who need their PDA closed may improve short-term respiratory outcomes. In our study, the 30 and 45-day cumulative incidence of extubation for infants referred for intervention before 14 days of life was decreased for those undergoing closure at a younger age (at 15 to 20 days of life, compared with 21 to 35 days of life).

Given the clinical importance of mitigating the consequences of PDA that may cause cardiopulmonary harm in premature infants, advances in how we define the timing for exposure may lead to more reliable detection and serial assessments of disease burden and inform decision-making processes. Variability remains on how a pathological PDA is defined and treated when the volume of the shunt is sufficiently large that cardiovascular compromise may ensue, especially for infants who have been mechanically ventilated for a prolonged period. As such, reducing the total number of ventilator days by expeditious PDA closure may ultimately improve both short- and long-term outcomes.

There were several limitations to this study. Intervention timing was not assigned randomly and the potential for unmeasured confounding existed, especially without the ability to adjust for possible post-baseline confounders. The decision for the neonates receiving late intervention was based on the treating physician's discretion and logistical restraints. However, the specific reasons were unavailable to the researchers. Furthermore, there may be situations in which the decision to intervene against PDA is not captured in the available data or based on clinician's bedside discretion in such a way that lacks equipoise. We tried to limit this occurrence by implementing relatively strict eligibility criteria and we attempted to emulate the randomization of treatment strategy by including baseline covariates of birth weight, gestational age, age at referral, sex, year of referral, and whether the patients had had pharmacological treatments for PDA at referral in the treatment model. However, we did not have access to information on several potentially relevant baseline and post-baseline confounders (i.e., echocardiogram and ventilator settings at referral, BPD, and associated pulmonary hypertension). Loss to follow-up due to retro-transfer after intervention was frequent and may have introduced bias. Finally, the small sample size precluded sensitivity analysis stratified by the number of PDA medical treatment courses, closure type (thoracotomy vs. transcatheter), or referral year.

5. Conclusions

In summary, we specified and then emulated a target trial related to the timing of PDA closure using data from electronic health records. This analysis suggests that an early PDA closure strategy following referral for a definitive procedure may be associated with short-term respiratory benefit among premature infants with symptomatic PDA; however, due to the imprecision of the estimates, 95% confidence

intervals were compatible with earlier extubation in either treatment strategy. For future directions, we could investigate the effect using a larger dataset after including echocardiography parameters and ventilator settings into the treatment model. We could also focus on examining long-term outcomes such as the risk of BPD or mortality. This would provide a more comprehensive understanding of the effect of the timing of the definitive procedural closure of PDA.

Author Contributions: Conceptualization, Z.D. and A.L.M.; methodology, Z.D., A.L.M., P.T.L., and C.R.W.; analysis, Z.D. and A.L.M.; writing—original draft preparation, Z.D., A.L.M., P.T.L., C.R.W., M.F., and D.P.; writing—review and editing, Z.D., A.L.M., P.T.L., C.R.W., D.P, and M.F. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Boston Children’s Hospital (Protocol number IRB-P00035857, approved on 25 September 2020).

Informed Consent Statement: Patient consent was waived due to the retrospective study design.

Data Availability Statement: All data have been presented in this study. Further inquiry can be directed to the corresponding author. The code used in this analysis is available online: <https://github.com/zhou996996/PDA-timing-study/tree/main> (accessed on 13 May 2025).

Conflicts of Interest: CRW discloses their relationships with Bunnell Inc and HydroSpire Medical. PTL discloses their relationships with Abbot Congenital. There are no conflicts of interest declared by the other authors.

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Supplementary Materials

Table S1: Variables used in the analysis when emulating the target trial.

Table S2: Summary of echocardiogram parameters from the last assessment before PDA intervention among eligible individuals who were referred for intervention for PDA closure, at the end of the grace period.

Table S3: Summary of events and outcome among eligible individuals who were referred for intervention for PDA closure, at the end of the grace period.

Table S4. Estimated cumulative incidence of extubation and difference at selected time points for sensitivity analyses 1 and 2;

Figure S1. Estimated cumulative incidence and cumulative incidence difference of extubation since referral for patent ductus arteriosus intervention, comparing early (0–4 days from referral) with late (5–14 days from referral) interventions, with analysis treating death as a censoring event (sensitivity analysis #1).

Figure S2. Estimated cumulative incidence and cumulative incidence difference of extubation since referral for patent ductus arteriosus intervention, comparing early (0–4 days from referral) with late (5–14 days from referral) interventions, with analysis including referral site in the confounder set (sensitivity analysis #2).

Table S1. Details of covariates used in the estimation of inverse probability weights in the main analysis.

Variable	Functional form	Value
Gestational age (days)	Splines	Continuous
Age at referral (weeks)	Splines	Continuous
Female	Indicator	Binary
Birth weight (grams)	Splines	Continuous
Pharmacologic intervention for PDA	Indicator	Binary
Follow-up time (days)	Splines	Continuous
Year of referral	Splines	Continuous

Table S2. Summary of echocardiogram parameters from the last assessment before PDA intervention among eligible individuals who were referred for intervention for PDA closure, stratified by intervention status at the end of the grace period. Data presented as median (interquartile range) or number (percent); PDA, patent ductus arteriosus.

	Early group <i>n</i> =70 Unweighted	Late group <i>n</i> =38 Unweighted	Early group <i>n</i> =166 Weighted	Late group <i>n</i> =94 Weighted
Age at echocardiogram, days	21.0 [14.0, 27.0]	22.5 [14.5, 30.8]	19.0 [14.0, 26.0]	23.0 [16.0, 28.0]
Diameter of duct, mm*	2.5 [2.2, 3.0]	2.4 [2.0, 2.5]	2.4 [2.0, 2.9]	2.5 [2.0, 3.0]
Peak systolic velocity of shunt, mm Hg*	20.0 [15.0, 25.0]	20.0 [15.0, 35.0]	20.6 [15.0, 25.0]	21.9 [15.0, 25.0]
Retrograde diastolic flow in Doppler (%)*	45 (76.3)	14 (50.0)	85 (76.2)	56 (70.4)
Dilation of left atrium (%)*	50 (72.5)	24 (66.7)	96 (58.5)	65 (71.0)
Dilation of left ventricle (%)*	49 (72.1)	19 (52.8)	86 (52.3)	62 (68.3)

*Missing data: diameter of duct (*n*=15, 11%), peak systolic velocity of shunt (*n*=57, 43%), retrograde diastolic flow in Doppler (*n*=28, 21%), dilation of the left atrium (*n*=4, 3%), and dilation of the left ventricle (*n*=5, 4%).

Table S3. Summary of events and outcome among eligible individuals who were referred for intervention for PDA closure, stratified by intervention status at the end of the grace period.

	Early group <i>n</i> =70 Unweighted	Late group <i>n</i> =38 Unweighted
Transcatheter closure (%)	20 (28.6)	12 (31.6)
Intervention since referral, days	1.0 [1.0, 3.0]	8.0 [6.8, 10.0]
Mechanical ventilation since referral, days	6.0 [4.0, 33.8]	16.0 [10.5, 32.8]
Intervention day of age, days	21.0 [14.0, 27.0]	22.5 [14.5, 30.8]
Event (%)		
Extubation	23 (32.9)	24 (63.2)
Lost to follow-up*	33 (47.1)	9 (23.7)
Death	2 (2.9)	1 (2.6)
Administrative censoring	12 (17.1)	4 (10.5)

Data presented as median (interquartile range) or number (percent).

*Lost to follow-up was due to retrotransfer.

Table S4. Estimated cumulative incidence of extubation and difference at selected time points for sensitivity analyses 1 and 2.

	Day 7	Day 14	Day 30	Day 45
Sensitivity analysis 1: truncating the follow-up at time of death for 3 death cases				
Early PDA intervention (%)	21 (6, 47)	38 (10, 72)	55 (22, 83)	64 (30, 87)
Late PDA intervention (%)	6 (2, 12)	16 (6, 39)	55 (18, 89)	77 (2, 98)
Difference (ref. late) (%)	15 (0, 42)	22 (-11, 56)	0 (-46, 46)	-12 (-52, 40)
Sensitivity analysis 2: including referral site in the confounder set				
Early PDA intervention (%)	31 (5, 78)	52 (10, 94)	65 (23, 95)	72 (35, 96)
Late PDA intervention (%)	6 (0, 14)	15 (2, 60)	48 (6, 99)	66 (7, 100)
Difference (ref. late) (%)	25 (-1, 74)	36 (-18, 80)	18 (-44, 67)	6 (-47, 70)

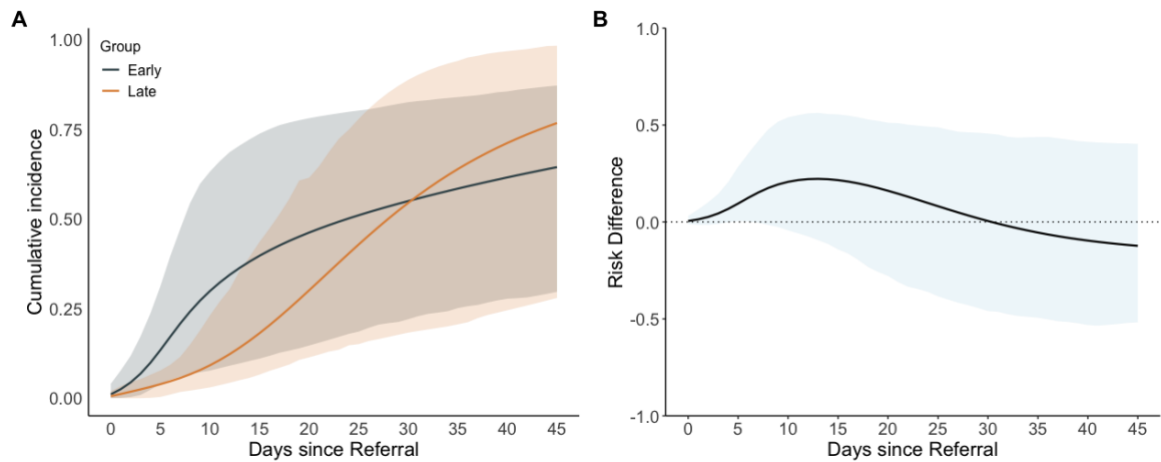


Figure S1. Estimated cumulative incidence and cumulative incidence difference of extubation since referral for patent ductus arteriosus intervention, comparing early (0-4 days from referral) with late (5-14 days from referral) interventions, with analysis treating death as a censoring event (sensitivity analysis #1). **(A)** Estimated cumulative incidence (95% confidence interval shaded); **(B)** Estimated cumulative incidence difference (95% confidence interval shaded), using the late group as the reference.

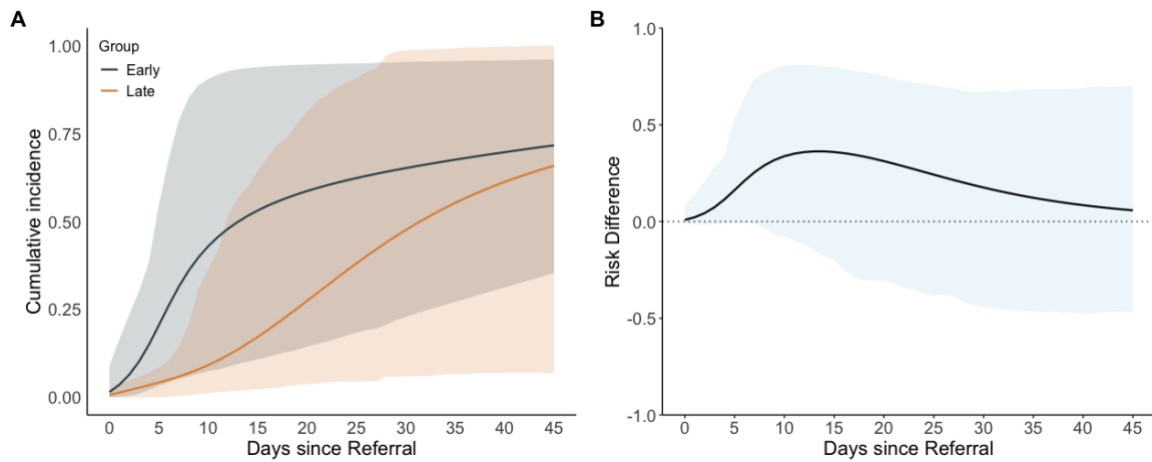


Figure S2. Estimated cumulative incidence and cumulative incidence difference of extubation since referral for patent ductus arteriosus intervention, comparing early (0-4 days from referral) with late (5-14 days from referral) interventions, with analysis including referral site in the confounder set (sensitivity analysis #2). **(A)** Estimated cumulative incidence (95% confidence interval shaded); **(B)** Estimated cumulative incidence difference (95% confidence interval shaded), using the late group as the reference.

Project 2

A Target Trial Emulation Comparing High-frequency Jet Ventilation Management Strategies for Respiratory Acidosis among Neonates with Respiratory Failure

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Keywords: High-frequency jet ventilation, hypercapnia, respiratory failure, neonate, target trial emulation, inverse probability weighting, dynamic treatment strategies

Abstract

Background: Rescue high-frequency jet ventilation (HFJV) is widely used in neonatal intensive care units (NICUs) to treat respiratory failure. However, there is no consensus on PIP management strategies for respiratory acidosis for neonates undergoing HFJV for the first time, as clinicians balance efficient correction of acidosis with avoiding abrupt changes in $p\text{CO}_2$ that may contribute to neurovascular injury.

Methods: First, we specified the protocol of a hypothetical randomized trial (the “target trial”) that would estimate the effect on pH, $p\text{CO}_2$, and extubation of progressive (increasing PIP by 1-2 cmH_2O within a 1-to-2 hour interval) vs. conservative (increasing PIP by more than 2 cmH_2O within a 1-to-2 hour interval) PIP management strategies when $\text{pH} < 7.25$ in acidotic neonates after HFJV initiation. Then we explicitly emulated this target trial and estimated the observational analog of the per-protocol effect of following each of these strategies using electronic health records via IP weighting to adjust for baseline and time-varying confounding.

Results: A total of 225 neonates and infants met the eligibility criteria between September 2011 and January 2023. Twelve hours after initiation of HFJV, 123 and 110 neonates were compatible with the conservative and progressive PIP management strategies, respectively. Changes in pH and $p\text{CO}_2$ (from baseline of the initial value on HFJV) were of greater magnitude in the progressive group compared with the conservative group, with maximum difference occurring at hour 6 (pH: 0.23 [95%CI, 0.04 to 0.32]; $p\text{CO}_2$: -34 [95%CI, -52 to -3]). The neonates in the progressive group

generally extubated sooner than in the conservative group, with the maximum cumulative incidence difference occurring at day 29 (30 percentage points; 95% CI, -44 to 68).

Conclusions: By explicitly emulating a target trial using electronic health records and applying IP weighting, we compared real-world dynamic PIP management strategies for neonates who initiated HFJV. Neonates who initiated HFJV managed with a progressive strategy appeared to experience greater changes in pH and pCO₂ and may be associated with earlier extubation than those managed with a conservative strategy.

1. Introduction

High-frequency jet ventilation (HFJV) is often used in neonatal intensive care units (NICUs) to treat respiratory failure in premature infants as a lung protective strategy (1,2). For neonates who have initiated HFJV for hypercarbic respiratory failure, clinicians attempt to manage the ventilator in such a way that the partial pressure of CO₂ (pCO₂) decreases gradually. A large magnitude rapid correction in pCO₂ can cause cerebrovascular spasm and predispose to neurovascular injury.

As such, HFJV is often initiated with an initial peak inspiratory pressure (PIP) set slightly higher than the PIP on the conventional ventilator (1,2). Once initial PIP is set, it is then incrementally titrated to achieve acceptable pCO₂ and pH levels (1). Specific management of HFJV PIP varies across institutions (3–7) and it is not known if larger magnitude increases in PIP cause unacceptably rapid changes in pCO₂ and pH. In this manuscript, we use electronic health records data to emulate a target trial comparing two PIP titration strategies.

2. Methods

2.1 Specification of the Target Trial

We first specify the protocol of the hypothetical randomized trial (the “target trial”) that would estimate the effect of PIP titration strategies. Specifically, for acidotic individuals with pH < 7.25, the first strategy would titrate PIP by increments of 1 or 2 cmH₂O, while the second strategy would titrate PIP by increments of 3 cmH₂O or more. **Table 1** summarizes the key components of the protocol of this target trial.

Eligibility criteria

Neonates would be eligible for this study if they initiate treatment with HFJV. Individuals would be excluded if they have been treated with ECMO prior to HFJV, have a history of HFJV use, weigh more than 6 kg, have a tracheostomy, or lack baseline pH or ventilator parameters.

Table 1. Specification of the target trial and description of its emulation

Protocol component	Specification of the target trial	Target trial emulation
Eligibility criteria	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> - Neonates (age <6 months) who initiate treatment with HFJV <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> - Prior use of ECMO - Prior use of HFJV - Tracheostomy - Body weight > 6 kg - Missing baseline pH or ventilator parameters 	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Neonates (age <6 months) who initiated HFJV at Boston Children’s Hospital from September 2011 to January 2023
Monitoring and treatment strategies	<ol style="list-style-type: none"> 1) Undergo “conservative” PIP titration strategy (increasing by 1-2 cmH₂O within 1 to 2 hours) when pH < 7.25 2) Undergo “progressive” PIP titraion strategy (increasing by 3 cmH₂O or more within 1 to 2 hours) when pH < 7.25 <p>Follow the assigned strategy for the first 8 hours of HFJV treatment (first 12 hours of HFJV treatment for outcome of extubation)</p>	Same as the target trial
Treatment assignment	Random assignment to a treatment arm without blinding	Each individual is classified into both strategies at baseline
Outcome	<p>Primary outcomes:</p> <ul style="list-style-type: none"> - pH change from baseline at 2, 4, 6 and 8 hours - Extubation over 45 days follow-up 	Same as target trial

	Secondary outcome:	
	- pCO ₂ change from baseline at 2, 4, 6 and 8 hours	
Follow-up period	Primary outcomes:	Same as target trial
	- Follow-up begins at the time of assignment and ends at 8 hours (for outcome of pH change), or at 45 days or death, whichever occurs first (for outcome of extubation)	
	Secondary outcome:	
	- Follow-up begins at the time of assignment and ends at 8 hours	
Causal contrast	Per-protocol effect	Observational analog of per-protocol effect
Analysis plan	Per-protocol analysis: individuals are censored beginning at any point they do not adhere to their treatment assignment. Inverse probability weighting is used to avoid selection bias caused by the artificial censoring process.	Same as target trial with the following modification for IP weighting: Since treatment assignment is unknown, eligible individuals contribute clones to each treatment arm. A given clone is censored at the time of deviation from the assigned treatment strategy.

ECMO, extracorporeal membrane oxygenation; HFJV, high-frequency jet ventilation; PIP, peak inspiratory pressure; pCO₂, partial pressure of CO₂.

Treatment strategies

For the first 12 hours of treatment with HFJV, eligible participants would be assigned to a strategy of either:

(1) a “conservative” PIP management strategy (increasing PIP by 1-2 cmH₂O within 1 to 2 hours), or

(2) a “progressive” PIP management strategy (increasing PIP by 3 cmH₂O or more within 1 to 2 hours),

when pH falls below 7.25. Ventilator parameters and physiologic variables would serially be measured and recorded prior to HFJV initiation and at 1, 2, 4, 6, 8 and 12 hours afterward. Measurement of blood gas would be left to the discretion of treating clinicians. For either strategy, the specific level of PIP change would be determined by the treating physician.

Treatment assignment

Treatment would be assigned randomly in a non-blinded fashion.

Outcome

The primary outcomes include: 1) pH change from baseline (defined as 1 hour on HFJV) at 2, 4, 6, and 8 hours of randomization; 2) successful extubation, defined as no invasive mechanical ventilation for at least 7 days after extubation (8). The secondary outcome is pCO₂ change from baseline (defined as 1 hour on HFJV) at 2, 4, 6, and 8 hours of randomization

Follow-up

The follow-up period would begin at randomization. For the outcomes of changes in pH and pCO₂, follow-up would end at 8 hours and outcomes for individuals who died prior to 6 hours would be censored. For the outcome of extubation, follow-up would end at 45 days. An individual who died prior to extubation was considered to be intubated until the end of the follow-up period (corresponding to a total effect type of estimand).

Casual contrast

We would also estimate a per-protocol effect (specifically, the effect of adhering to the assigned treatment with complete adherence).

Analysis

To estimate this per-protocol effect using data from the target trial, for the outcome of pH and pCO₂ change, we would fit a treatment model over 8 hours from initiation of HFJV for each intervention among all eligible individuals, censoring those who had not adhered to their assigned treatment arm at the time of first deviation from the protocol. For the outcome of extubation, we would fit a treatment model over 12 hours. Both models would adjust for baseline and post-baseline prognostic factors that predict adherence to the assigned treatment strategy. In this case, the adjustment set would include baseline covariates of body weight at HFJV, post-menstrual age at HFJV, sex, and year at HFJV, and time-varying covariates of blood gas and ventilator parameters (e.g., pH, blood gas type, PEEP, HFJV PIP, Servo pressure, and FiO₂) prior to change in PIP. Importantly, the blood gas and ventilator settings would be the most recent readings, with blood gas samples collected just before any adjustment to the ventilator settings. We would then estimate inverse probability of treatment weights from the treatment models and, subsequently, fit weighted pooled regression models to estimate changes in pH and pCO₂ from hour 1 over 8 hours, and cumulative incidence of extubation over 45 days. Details are described in the Appendix.

For the outcome of pH change, we would conduct two sensitivity analyses. First, we would repeat the main analysis by including RDS of prematurity and air leak syndrome in the confounder set of the treatment model. Second, we would restrict the analysis to the neonates with no record of congenital heart disease at baseline. For the outcome of extubation, we would conduct the same sensitivity analyses as for the outcome of pH change. We would additionally estimate the controlled direct effect (as compared with the total effect of the main analysis), or the effect had no competing risk events occurred (i.e., had no participants died).

2.2 Emulation of the Target Trial

This study was approved by the Boston Children's Hospital Institutional Review Board. We analyzed data from a single-institution registry of all neonates who initiated high-frequency ventilation at Boston Children's Hospital from 2012. Demographic, clinical, HFJV settings, and blood gas data had been entered into the database.

The eligibility criteria, monitoring and treatment strategies, follow-up, and outcomes were the same as those specified in the target trial above. We note several differences in the target trial emulation.

Treatment assignment

Each eligible participant was classified into both strategies at baseline.

Causal contrast

The casual contrast was an observational analog of the per-protocol effect.

Analysis

The analysis of the per-protocol effect analog followed that of the target trial with the following exception. Unlike in the target trial, in the observed data, an individual's data at baseline may be consistent with more than one of the two strategies of interest. That is, during the first 8 hours (for the outcome of pH and pCO₂ change) or 12 hours (for the outcome of extubation) from initiation of HFJV, a participant's observed data may at times be consistent with both strategies. We created two clones of each individual and assigned one clone to each of the two treatment strategies. Each eligible patient contributes one clone to each treatment arm so long as they remain compatible with that strategy. Clones would then be censored when they deviated from the assigned treatment strategies, or PIP was not increased when pH < 7.25. Clones would be considered compliant to the assigned strategy when pH ≥ 7.25, regardless of PIP change, or when PIP reached its maximum (50 cmH₂O) (1). The probability of a clone remaining uncensored at each time epoch equals the probability of adhering to the assigned treatment strategy based on the past covariates. The treatment model was used to estimate the probability of being adhering to assigned treatment strategies, which was used to derive IP weights. RStudio (version 2023.06.1+524) was used for the analysis.

3. Results

In the emulation of the target trial, a total of 225 neonates met the eligibility criteria between September 2011 and January 2023. Twelve hours after initiation of HFJV, 123 and 110 neonates and infants had histories consistent with the conservative and progressive PIP management strategies, respectively. **Figure 1** displays a flowchart of the study population.

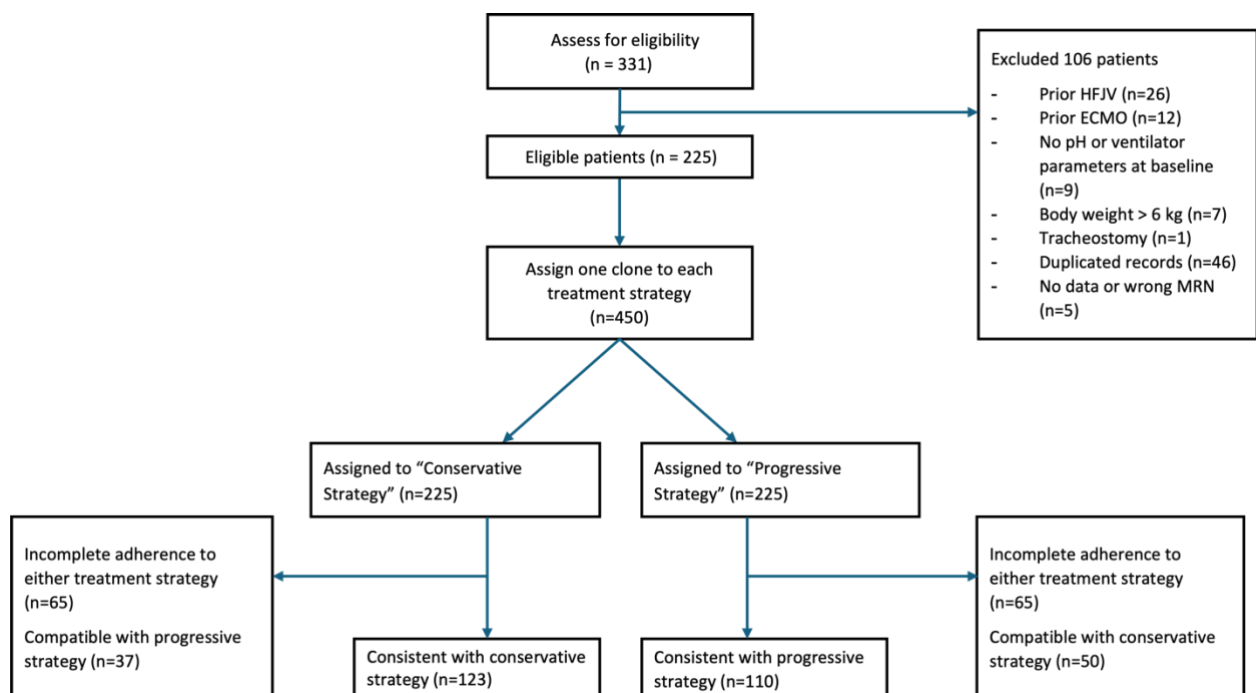


Figure 1. Study flowchart.

The proportion of female patients (42% vs. 41%) and median post menstrual age (34 weeks vs. 36.4 weeks) at the time of HFJV initiation were similar in the conservative group and the progressive group. The body weight at the time of HFJV was slightly lower in the conservative group (2 kg) than in the progressive group (2.5 kg). The top three reasons for HFJV were the same in the conservative group and progressive group: RDS of prematurity (51% vs. 46%), congenital heart disease (20%

vs. 19%), and persistent pulmonary hypertension/meconium aspiration syndrome (12% vs. 18%). Twenty-seven (22%) and 30 (27%) neonates had air leak syndrome in the conservative and progressive group, respectively (**Table 2**). Baseline pH (7.33 vs. 7.31) and pCO₂ (52 vs. 55 mmHg) (1 hour since HFJV) were also similar in the conservative group and progressive group. The other initial HFJV settings and blood gas parameters at baseline (1 hour since HFJV) were presented in **Table S2**.

Table 2. Demographics and clinical characteristics at initiation of HFJV of adherent patients, stratified by intervention at the end of 12 hours from HFJV initiation.

	Conservative <i>n</i> =123 Unweighted	Progressive <i>n</i> =110 Unweighted	Conservative <i>n</i> =1370 Weighted	Progressive <i>n</i> =24436 Weighted
PMA at HFJV*, wks	34 [28.4, 38]	36.4 [29.7, 40]	29.3 [27.9, 36]	34.6 [27.3, 39.4]
Female* (%)	51 (42)	45 (41)	752 (55)	10836 (44)
Body weight at HFJV*, kg	2 [1, 3.1]	2.5 [1.3, 3.5]	1.1 [0.8, 1.8]	2.5 [1, 3.2]
Year at HFJV*	2017 [2015, 2019]	2017 [2014, 2019]	2018 [2017, 2020]	2018 [2014, 2019]
Primary diagnosis (%)				
RDS of prematurity**	63 (51)	50 (46)	942 (69)	13633 (56)
PPHN/MAS	15 (12)	20 (18)	42 (3)	5361 (22)
CHD	24 (20)	21 (19)	154 (11)	2607 (11)
Air leak syndrome** (%)	27 (22)	30 (27)	328 (24)	10408 (43)
Pneumothorax (%)	24 (20)	27 (25)	318 (23)	5707 (23)
Pulmonary interstitial emphysema (%)	2 (2)	2 (2)	10 (1)	2112 (9)
pH				
Pre-HFJV	7.17 (0.12)	7.2 (0.12)	7.14 (0.08)	7.17 (0.1)
Baseline †	7.33 (0.13)	7.31 (0.14)	7.31 (0.12)	7.15 (0.07)
pCO ₂ , mmHg				
Pre-HFJV	75 (24)	73 (25)	76 (18)	77 (17)
Baseline †	52 (21)	55 (23)	50 (19)	77 (15)

Median (interquartile range), mean (standard deviation) or number (%); PMA, postmenstrual age; HFJV, high-frequency jet ventilation; RDS, respiratory distress syndrome; PPHN, persistent pulmonary

hypertension; MAS, meconium aspiration syndrome; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease.

* Time-fixed covariates adjusted in the treatment model in the main analysis.

** Time-fixed covariates adjusted in the treatment model in the sensitivity analysis 2.

† Within 1 hour from HFJV start.

3.1 Primary outcome - pH change (main analysis)

The estimated pH levels in the progressive group were higher than in the conservative group since 4 hours after HFJV initiation. The estimated average pH change from baseline in the progressive group remained higher than in the conservative group. The differences were 0.17 (95% CI, -0.02 to 0.31), 0.15 (95% CI, 0.04 to 0.29), 0.23 (95% CI, 0.04 to 0.32), and 0.21 (95% CI, 0.06 to 0.38) at 2, 4, 6, and 8 hours after HFJV initiation, respectively (**Figure 2** and **Table 3**).

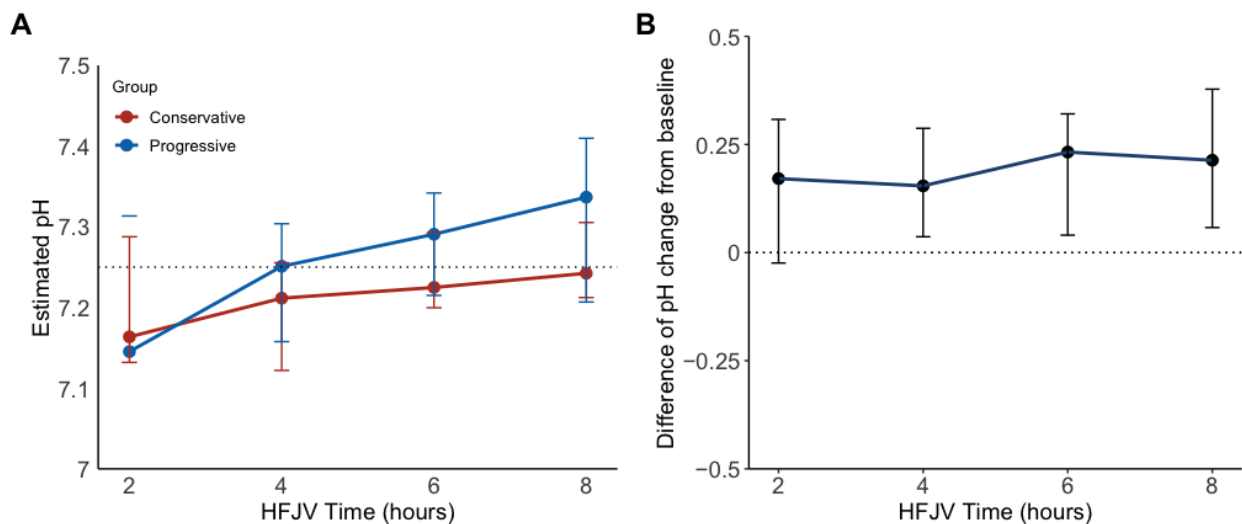


Figure 2. Estimated pH and differences of pH change from baseline (1 hour since HFJV) at selected time points, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O). (A) Estimated pH (95% confidence interval showed); (B) Estimated differences of pH change from baseline (95% confidence interval showed), using the conservative group as the reference.

Table 3. Estimated pH and pCO₂ and the differences of change from baseline (1 hour since HFJV) at selected time points.

	Hour 2	Hour 4	Hour 6	Hour 8
pH				
Conservative strategy	7.16 (7.13, 7.29)	7.21 (7.12, 7.26)	7.22 (7.2, 7.29)	7.24 (7.21, 7.31)
Progressive strategy	7.15 (6.95, 7.31)	7.25 (7.16, 7.3)	7.29 (7.21, 7.34)	7.34 (7.21, 7.41)
Difference of change from baseline (ref. cons)	0.17 (-0.02, 0.31)	0.15 (0.04, 0.29)	0.23 (0.04, 0.32)	0.21 (0.06, 0.38)
pCO₂				
Conservative strategy, mmHg	69 (47, 74)	64 (57, 76)	62 (52, 68)	62 (51, 65)
Progressive strategy, mmHg	67 (46, 86)	61 (47, 75)	56 (47, 70)	47 (39, 63)
Difference of change from baseline (ref. cons), mmHg	-20 (-49, 10)	-22 (-50, -5)	-34 (-52, -3)	-31 (-65, -5)

3.2 Primary outcome – Extubation (main analysis)

Using the same treatment model as the main analysis of pH change, the cumulative incidence of extubation was higher in the progressive group than in the conservative group throughout the study period. At day 14 from HFJV initiation, the cumulative incidence of extubation was 32% (95% CI, 0 to 81%) in the progressive group and 13% (95% CI, 4 to 29%) in the conservative group with a cumulative incidence difference of 19 percentage points (95% CI, -22 to 69). At the end of follow-up period, the cumulative incidence of extubation was 75% (95% CI, 0 to 100%) in the progressive group and 61% (95% CI, 44 to 84%) in the conservative group, with a cumulative incidence difference of 14 percentage points (95% CI, -77 to 48). The maximum cumulative incidence difference occurred at day 29 (30 percentage points; 95% CI, -44 to 68). The cumulative incidence of extubation over the 45-day follow-up period and cumulative incidence differences are illustrated in **Figure 3** and **Table 4**.

Additionally, the estimated average ventilator days were lower in the progressive group than in the conservative group at each time point (**Table S3**).

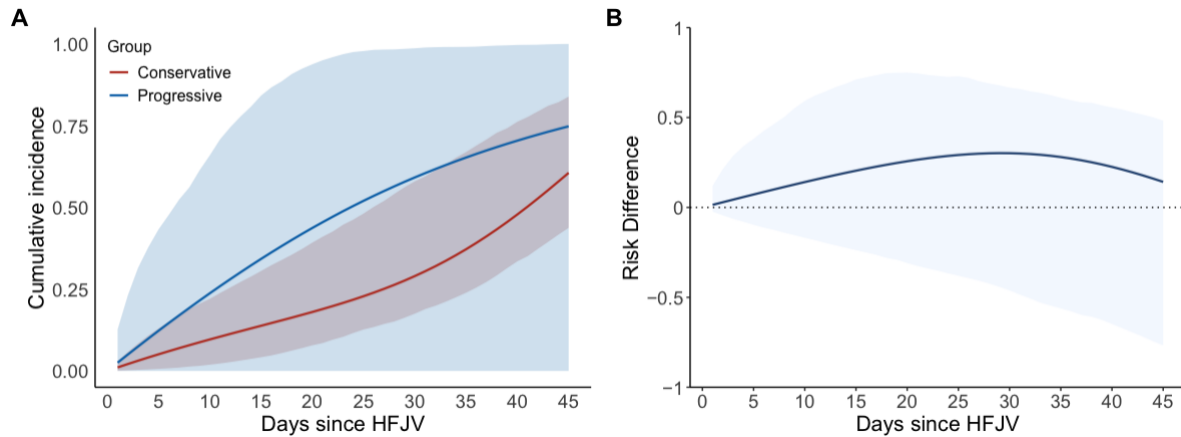


Figure 3. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O). (A) Estimated cumulative incidence (95% confidence interval shaded); (B) Estimated cumulative incidence difference (95% confidence interval shaded), using the conservative group as the reference.

Table 4. Estimated cumulative incidence of extubation and differences at selected time points.

	Day 7	Day 14	Day 21	Day 30	Day 45
Conservative strategy (%)	7 (1, 17)	13 (4, 29)	19 (9, 41)	29 (18, 58)	61 (44, 84)
Progressive strategy (%)	17 (0, 52)	32 (0, 81)	45 (0, 95)	59 (0, 99)	75 (0, 100)
Difference (ref. cons) (%)	10 (-12, 46)	19 (-22, 69)	27 (-33, 75)	30 (-46, 67)	14 (-77, 48)

3.3 Secondary outcome – pCO₂ change

The estimated pCO₂ remained lower in the progressive group than in the conservative group. The estimated average changes in pCO₂ change from baseline were of greater magnitude in the progressive group than in the conservative group, consistent with the findings of pH change. The differences were -20 (95% CI, -49 to

10), -22 (95% CI, -50 to -5), -34 (95% CI, -52 to -3), and -31 (95% CI, -65 to -5) mmHg at 2, 4, 6, and 8 hours after HFJV initiation, respectively (**Figure 4** and **Table 3**).

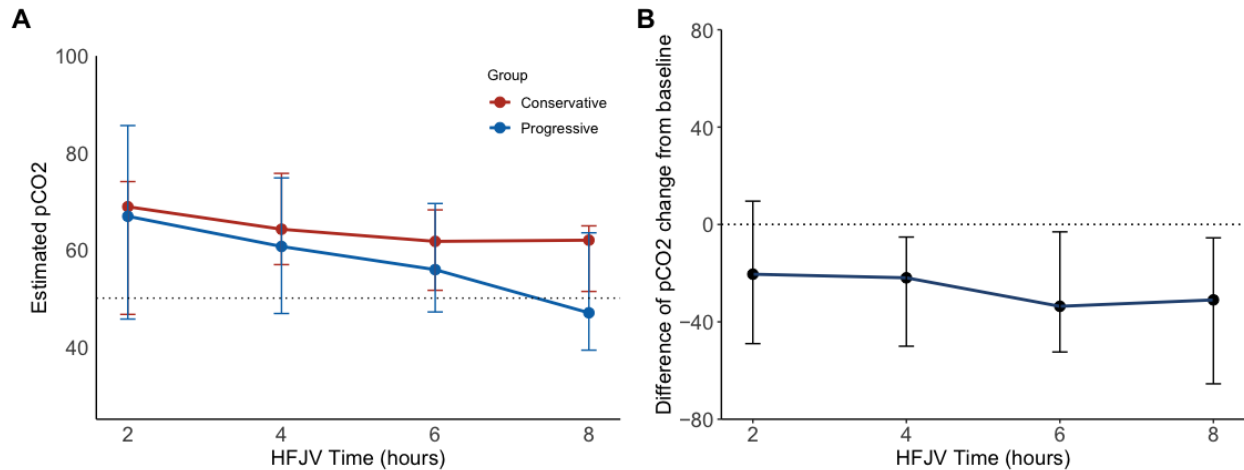


Figure 4. Estimated pCO₂ and differences of pCO₂ change from baseline (1 hour since HFJV) at selected time points, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O). **(A)** Estimated pCO₂ (95% confidence interval showed); **(B)** Estimated difference of pCO₂ change from baseline (95% confidence interval showed), using the conservative group as the reference.

3.4 Sensitivity analyses

For the outcome of pH change, the findings of sensitivity analyses 1 (repeating the main analysis by including RDS of prematurity and air leak syndrome in the adjustment set of the treatment model) and 2 (restricting the analysis to the neonates with no records of congenital heart disease at baseline) aligned with those of the main analysis. The estimated average pH change from baseline remained higher in the progressive group compared to the conservative group. Results from sensitivity analysis 1 are presented in **Figure S1** and **Table S4**, and sensitivity analysis 2 in **Figure S2** and **Table S4**.

For the outcome of extubation, the results of the sensitivity analyses 4 (estimating the effect had no competing risk events occurred), 5 (repeating the main analysis by including RDS of prematurity and air leak syndrome in the adjustment set of the treatment model), and 6 (restricting the analysis to the neonates with no records of congenital heart disease at baseline) were similar to those of the main analysis. Neonates and infants in the progressive intervention group were extubated sooner than those in the conservative intervention group until day 45. Results from sensitivity analysis 3 are presented in **Figure S3** and **Table S5**, sensitivity analysis 4 in **Figure S4** and **Table S5**, and sensitivity analysis 5 in **Figure S5** and **Table S5**. The events were summarized in **Table S6**.

4. Discussion

This paper describes the use of EHR data to emulate a target trial of ventilator management strategies. Our analysis suggests that, compared with acidotic neonates managed with conservative PIP strategy, the progressive strategy might be associated with earlier extubation in short-term at the expense of larger magnitude pH increase and pCO₂ decrease in the first few hours after HFJV initiation.

In our cohort, there were a large proportion of neonates ($n=73$, 32%) who did not have measured pH below 7.25 at any point and, therefore, were by definition adherent with both treatment arms throughout follow-up.

Traditional methods for confounding adjustment such as stratification would fail to properly account for confounding in the presence of treatment-confounder

feedback. PIP adjustment is a time-varying intervention that is altered by clinicians based on disease progression (pH and pCO₂) and response to prior treatment (PIP adjustment). Assessing such “dynamic” treatment strategies, which are sustained over time and adapt to the evolving characteristics and risk factors of patients, requires methodologies that account for treatment confounder feedback, such as IP weighting (9).

HFJV PIP is the primary determinant of V_T and CO₂ clearance, thus can help maintain target pCO₂ and pH levels. Titrating HFJV-PIP by 1 to 2 cmH₂O, 3 to 4 cmH₂O, or 5 to 6 cmH₂O can decrease pCO₂ by approximately 2 to 4 mmHg, 5 to 9 mmHg, and 10 to 14 mmHg, respectively (5). A progressive PIP weaning strategy is expected to reduce the time to extubation from HFJV, as an HFJV PIP of 20 cmH₂O or lower is a key extubation criterion (4). However, the effects of progressive PIP weaning when pH < 7.25 have not been previously evaluated. Here, we propose a method to compare the effect of different dynamic PIP management strategies in HFJV, particularly when conducting a randomized controlled trial is not feasible. The approach can further inform clinical decision-making process and optimize HFJV algorithm.

This study has several limitations. First, a key challenge in estimating the effects of dynamic treatment strategies using observational data is that only a few individuals may have data aligning with the intended strategies over the follow-up period (10), which is seen in our study - the number of individuals who remained consistent to their assigned treatment strategies 12 hours after HFJV treatment was limited. As a result, our findings were relatively imprecise. Second, timing of blood gas sampling

following HFJV treatment were determined at the clinician's discretion and influenced by logistical factors, leading to some missing data points of pH for some individuals. Third, arterial, capillary, and venous blood samples were collected to assess blood gas exchange in practice, though correlated, each with inherent physiological differences (11). Despite the differences, we applied the same pH threshold across all sample types, which may introduce variability to our analysis. To account for this, we incorporated blood gas type as a time-varying covariate in the treatment model. Finally, sensitivity analyses restricted to neonates with pH < 7.25 at hour 1 ($n=102$, 45%) or those with baseline air leak ($n=48$, 21%) were precluded due to limited sample sizes in these subgroups, despite their clinical relevance.

5. Conclusions

We described how to specify and emulate a target trial comparing conservative or progressive PIP management strategies for respiratory acidosis in neonates who underwent HFJV for the first time. Our study suggests that, compared to a conservative PIP titration strategy, the progressive approach might be associated with earlier extubation and a greater magnitude of rise in pH and drop in pCO₂ shortly after HFJV initiation, although 95% confidence intervals were compatible with earlier extubation with either strategy.

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Supplementary Materials

Table S1. Time fixed and time-varying variables used in the analysis for the outcomes of pH and pCO₂ change and extubation, when emulating the target trial.

Table S2. The initial HFJV settings and blood gas parameters at baseline (1 hour since HFJV) of adherent patients, stratified by intervention at the end of 12 hours from HFJV initiation.

Table S3. Weighted average ventilator days at selected time points.

Table S4. Estimated pH and the differences of change from baseline (1 hour since HFJV) at selected time points for sensitivity analyses 1 and 2.

Table S5. Estimated cumulative incidence of extubation and difference at selected time points for sensitivity analyses 3, 4, and 5.

Table S6. Summary of events among eligible individuals, stratified by intervention at the end of 12 hours from HFJV initiation.

Table S7. Demographics, clinical characteristics and the initial HFJV settings among included and excluded patients.

Figure S1. Estimated pH and differences of pH change from baseline (1 hour since HFJV) at selected time points, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis including RDS of prematurity and air leak syndrome in the confounder set (sensitivity analysis #1).

Figure S2. Estimated pH and differences of pH change from baseline (1 hour since HFJV) at selected time points, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis restricted to the neonates without congenital heart disease at baseline (sensitivity analysis #2).

Figure S3. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis treating death as a censoring event (sensitivity analysis #3).

Figure S4. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis including RDS of prematurity and air leak syndrome in the confounder set (sensitivity analysis #4).

Figure S5. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis restricted to the neonates without congenital heart disease at baseline (sensitivity analysis #5).

Table S1. Time fixed and time-varying variables used in the analysis for the outcomes of pH and pCO₂ change and extubation, when emulating the target trial.

Variable	pH and pCO ₂ change		Extubation	
	Functional form	Value	Functional form	Value
Time-fixed				
PMA at HFJV, wks	Splines	Continuous	Splines	Continuous
Female	Indicator	Binary	Indicator	Binary
Body weight at HFJV, kg	Splines	Continuous	Splines	Continuous
Year at HFJV	Splines	Continuous	Splines	Continuous
RDS of prematurity *	Indicator	Binary	Indicator	Binary
Air leak syndrome *	Indicator	Binary	Indicator	Binary
Time-varying [†]				
Time	Indicator	Categorical	Indicator	Categorical
pH	Linear and Quadratic	Continuous	Splines	Continuous
Blood gas type	Indicator	Categorical 1 – arterial, 2 – capillary, 3 - venous	Indicator	Categorical 1 – arterial, 2 – capillary, 3 - venous
PEEP, cmH ₂ O	Linear and Quadratic	Continuous	Splines	Continuous
HFJV PIP, cmH ₂ O	Linear and Quadratic	Continuous	Splines	Continuous
Servo pressure, psi	Linear and Quadratic	Continuous	Splines	Continuous
FiO ₂	Not included		Linear	Continuous

FiO₂, fraction of inspired oxygen; *PMA*, post menstrual age; *HFJV*, high-frequency jet ventilation; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure.

[†] Interaction terms are included for time and pH for the outcomes of pH and pCO₂ change and extubation.

* Adjusted in the sensitivity analyses 2 and 5.

Table S2. The initial HFJV settings and blood gas parameters at baseline (1 hour since HFJV) of adherent patients, stratified by intervention at the end of 12 hours from HFJV initiation.

	Conservative <i>n</i>=123 Unweighted	Progressive <i>n</i>=110 Unweighted	Conservative <i>n</i>=1370 Weighted	Progressive <i>n</i>=24436 Weighted
PaO ₂ *, mmHg	80.1 (58.2)	82.9 (58.2)	84 (36)	82 (25)
FiO ₂	0.6 (0.3)	0.7 (0.3)	0.6 (0.2)	0.6 (0.3)
HFJV PIP, cmH ₂ O	32.0 [28.0, 38.0]	34 [28.0, 39.8]	29 [26, 32]	33 [26, 37]
PEEP, cmH ₂ O	8 [7, 10]	8 [7, 10]	8 [7, 9]	8 [7, 9]
Frequency, breaths/min	420 [420, 420]	420 [420, 420]	420 [420, 420]	420 [420, 420]
Ontime *, second	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]
\bar{P}_{aw} *, cmH ₂ O	13.1 (3.2)	13.2 (3.1)	12.5 (2.3)	12.6 (2.5)
Servo pressure *, psi	3.5 (1.5)	3.7 (1.5)	2.8 (1.1)	2.9 (1)
OI *	14.0 (9.1)	14.5 (9.2)	12.3 (7.7)	11.2 (6.8)

Data is presented as mean (standard deviation) or median (Interquartile range); *HFJV*, high-frequency jet ventilation; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *FiO₂*, fraction of inspired oxygen; *OI*, oxygenation index; \bar{P}_{aw} , mean airway pressure.

* Missing data: PaO₂ (*n* = 103, 44%), ontime (*n* = 5, 2%), \bar{P}_{aw} (*n* = 2, 1%), and *OI* (*n* = 103, 44%).

Table S3. Weighted average ventilator days at selected time points.

	Day 7	Day 14	Day 21	Day 30	Day 45
Conservative strategy, days	6.9 (6.9, 7)	12.7 (11.8, 13.6)	17.7 (15.8, 19.6)	23.1 (19.7, 26.5)	30 (24.2, 35.8)
Progressive strategy, days	5.9 (4.8, 6.9)	10.1 (7.1, 13)	12.5 (8.1, 17)	15.5 (8.7, 22.4)	19.3 (9.3, 29.3)
Difference (ref. cons), days	-1.1 (-2.1, 0)	-2.7 (-5.7, 0.4)	-5.2 (-10.1, -0.3)	-7.6 (-15.2, 0.1)	-10.7 (-22.3, 0.9)

Mean (95% confidence interval).

Table S4. Estimated pH and the differences of change from baseline (1 hour since HFJV) at selected time points for sensitivity analyses 1 and 2.

	Hour 2	Hour 4	Hour 6	Hour 8
Sensitivity analysis 1: including RDS of prematurity and air leak syndrome in the confounder set				
Conservative strategy	7.16 (7.13, 7.29)	7.21 (7.12, 7.26)	7.22 (7.2, 7.29)	7.24 (7.21, 7.31)
Progressive strategy	7.15 (6.95, 7.31)	7.25 (7.16, 7.3)	7.29 (7.22, 7.34)	7.34 (7.21, 7.41)
Difference of change from baseline (ref. cons)	0.17 (-0.02, 0.31)	0.16 (0.03, 0.29)	0.23 (0.05, 0.32)	0.22 (0.06, 0.38)
Sensitivity analysis 2: restricted to the neonates without CHD at baseline				
Conservative strategy	7.16 (7.12, 7.34)	7.23 (7.11, 7.27)	7.22 (7.19, 7.28)	7.24 (7.19, 7.29)
Progressive strategy	7.31 (7.12, 7.35)	7.28 (7.15, 7.29)	7.27 (7.2, 7.34)	7.3 (7.21, 7.41)
Difference of change from baseline (ref. cons)	0.18 (-0.02, 0.31)	0.06 (0.01, 0.23)	0.15 (0.04, 0.3)	0.14 (0.06, 0.35)

CHD, congenital heart disease; RDS, respiratory distress syndrome.

Table S5. Estimated cumulative incidence of extubation and difference at selected time points for sensitivity analyses 3, 4, and 5.

	Day 7	Day 14	Day 21	Day 30	Day 45
Sensitivity analysis 3: truncating the follow-up at time of death for death cases					
Conservative strategy (%)	6 (1, 17)	13 (4, 30)	21 (9, 44)	35 (19, 66)	74 (53, 90)
Progressive strategy (%)	17 (0, 54)	32 (0, 84)	45 (0, 97)	59 (0, 99)	75 (0, 100)
Difference (ref. cons) (%)	11 (-13, 50)	19 (-24, 74)	24 (-37, 75)	23 (-55, 64)	1 (-85, 38)
Sensitivity analysis 4: including RDS of prematurity and air leak syndrome in the confounder set					
Conservative strategy (%)	7 (1, 17)	13 (4, 29)	18 (9, 42)	28 (17, 59)	59 (44, 85)
Progressive strategy (%)	16 (0, 53)	31 (0, 86)	45 (0, 98)	59 (0, 99)	75 (0, 100)
Difference (ref. cons) (%)	9 (-12, 48)	19 (-22, 75)	27 (-33, 75)	31 (-46, 67)	15 (-77, 48)
Sensitivity analysis 5: restricted to the neonates without CHD at baseline					
Conservative strategy (%)	5 (0, 17)	9 (2, 28)	14 (4, 37)	24 (10, 53)	60 (36, 83)
Progressive strategy (%)	23 (0, 55)	38 (0, 100)	51 (0, 100)	70 (0, 100)	98 (0, 100)
Difference (ref. cons) (%)	18 (-15, 50)	29 (-26, 80)	37 (-35, 81)	45 (-51, 74)	38 (-80, 57)

CHD, congenital heart disease; RDS, respiratory distress syndrome.

Table S6. Summary of events among eligible individuals, stratified by intervention at the end of 12 hours from HFJV initiation.

	Conservative <i>n</i>=123 Unweighted	Progressive <i>n</i>=110 Unweighted	Conservative <i>n</i>=1370 Weighted	Progressive <i>n</i>=24436 Weighted
Event (%)				
Extubation	57 (46)	57 (52)	652 (48)	19285 (79)
Death	20 (16)	20 (18)	266 (19)	127 (1)
Administrative censoring	28 (23)	18 (16)	309 (23)	2892 (12)
Lost to follow-up	18 (15)	15 (14)	144 (11)	2133 (9)

Number (%).

Table S7. Demographics, clinical characteristics and the initial HFJV settings among included and excluded patients.

	Included <i>n</i> =225 Unweighted	Excluded <i>n</i> =59 † Unweighted
PMA at HFJV, wks	33 [27.9, 37.6]	36 [29.4, 38.8]
Female (%)	90 (40)	24 (40.7)
Body weight at HFJV, kg	1.7 [0.8, 2.7]	2.2 [1, 3.4]
Year at HFJV	2018 [2015, 2019]	2019 [2017, 2020.5]
Primary diagnosis (%)		
RDS of prematurity	129 (57.3)	27 (45.8)
PPHN/MAS	25 (11.1)	2 (3.4)
CHD	36 (16)	10 (16.9)
Air leak syndrome (%)	48 (21.3)	13 (22.4)
Pneumothorax (%)	42 (18.7)	10 (16.9)
Pulmonary interstitial emphysema (%)	4 (1.8)	2 (3.4)
pH		
Pre-HFJV	7.15 (0.12)	7.16 (0.14)
Baseline †	7.26 (0.15)	7.29 (0.12)
pCO ₂ , mmHg		
Pre-HFJV	76 (23)	75 (22)
Baseline †	57 (23)	54 (17)
FiO ₂	0.62 (0.27)	0.73 (0.28)
HFJV PIP *, cmH ₂ O	31 [26, 37]	35 [29.5, 38]
PEEP *, cmH ₂ O	8 [7, 9]	8 [7, 10]
Servo pressure *, psi	3.1 (1.4)	3.7 (1.7)

Median (interquartile range), mean (standard deviation) or number (%); PMA, postmenstrual age; HFJV, high-frequency jet ventilation; RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension; MAS, meconium aspiration syndrome; CHD, congenital heart disease; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; FiO₂, fraction of inspired oxygen.

† Excluded duplicated patient records (n=46) and patient with wrong medical record number (n=1).

† Within 1 hour from HFJV start.

* Initial ventilator settings.

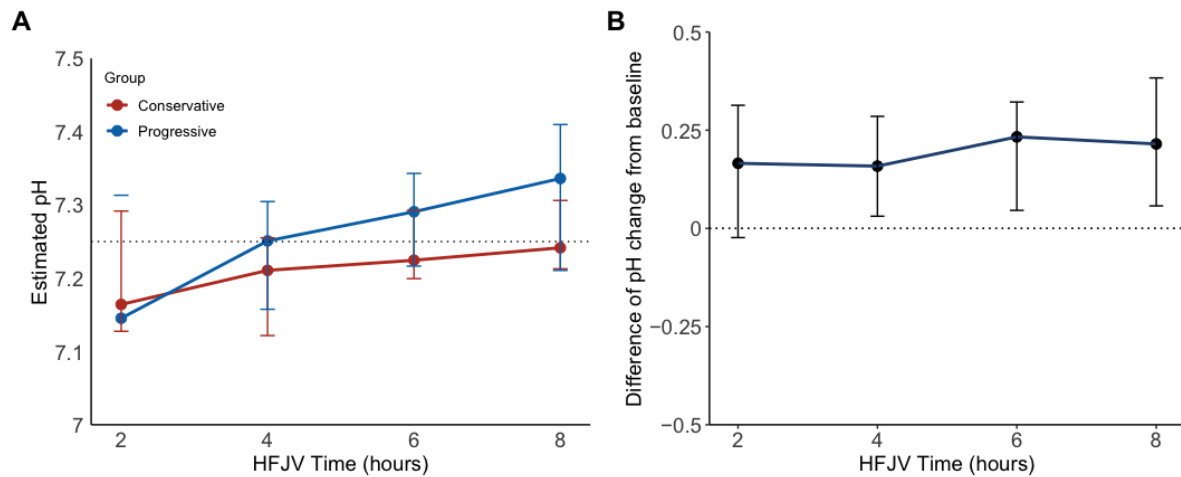


Figure S1. Estimated pH and differences of pH change from baseline (1 hour since HFJV) at selected time points, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis including RDS of prematurity and air leak syndrome in the confounder set (sensitivity analysis #1).

(A) Estimated pH (95% confidence interval showed); (B) Estimated differences of pH change from baseline (95% confidence interval showed), using the conservative group as the reference.

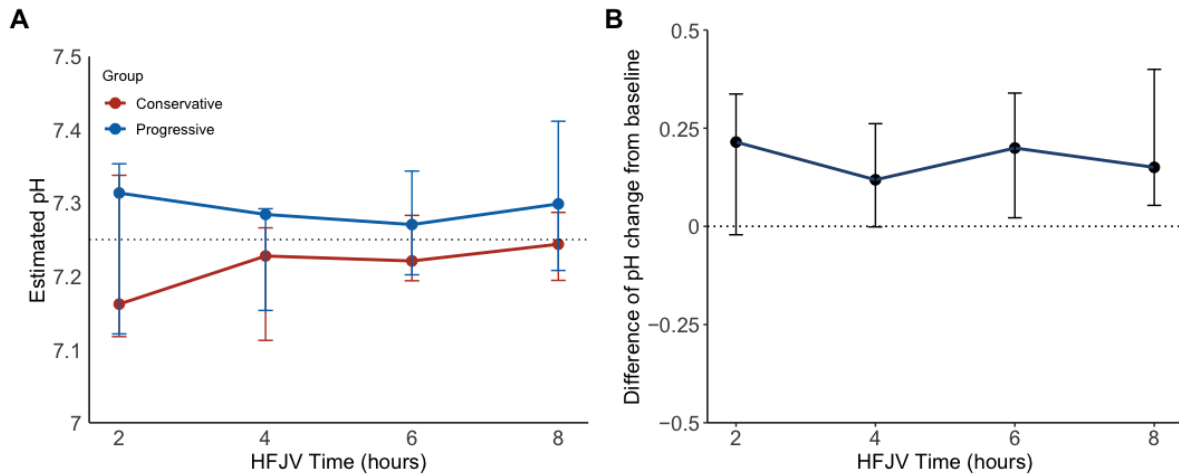


Figure S2. Estimated pH and differences of pH change from baseline (1 hour since HFJV) at selected time points, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis restricted to the neonates without congenital heart disease at baseline (sensitivity analysis #2).

(A) Estimated pH (95% confidence interval showed); (B) Estimated differences of pH change from baseline (95% confidence interval showed), using the conservative group as the reference.

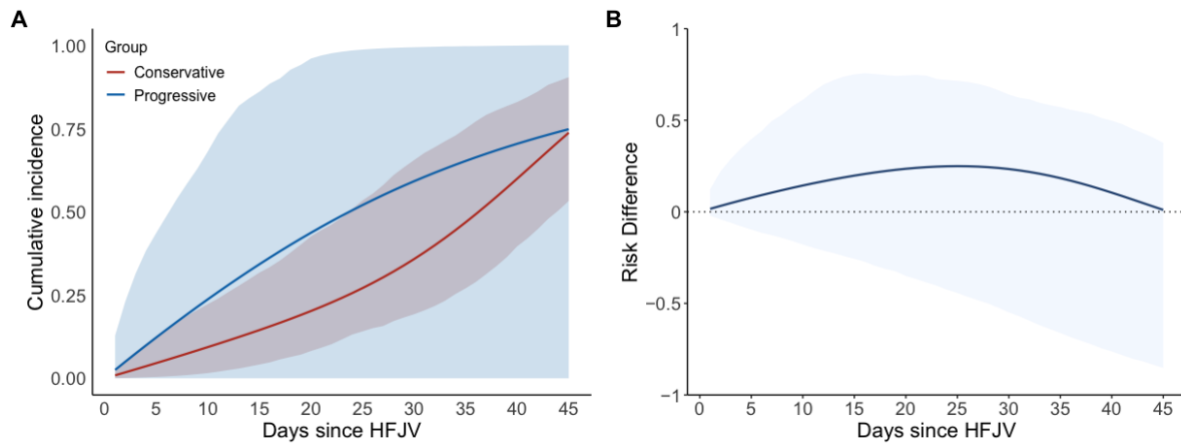


Figure S3. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis treating death as a censoring event (sensitivity analysis #3).

(A) Estimated cumulative incidence (95% confidence interval shaded); (B) Estimated cumulative incidence difference (95% confidence interval shaded), using the conservative group as the reference.

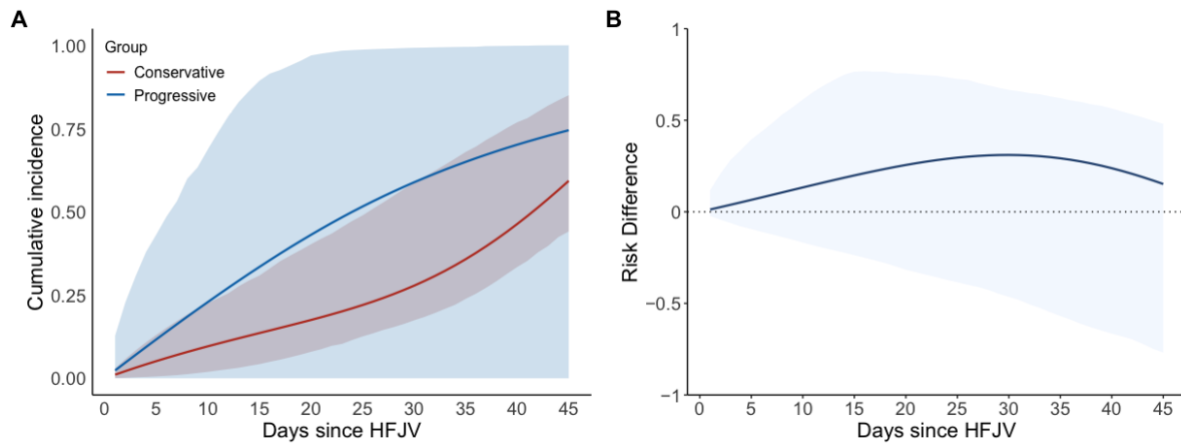


Figure S4. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis including RDS of prematurity and air leak syndrome in the confounder set (sensitivity analysis #4).

(A) Estimated cumulative incidence (95% confidence interval shaded); (B) Estimated cumulative incidence difference (95% confidence interval shaded), using the conservative group as the reference.

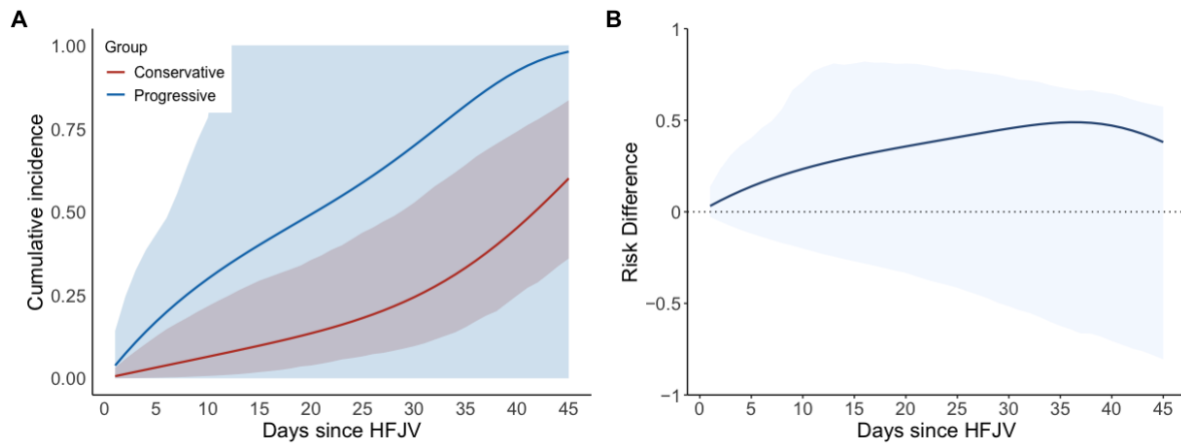


Figure S5. Estimated cumulative incidence and cumulative incidence difference of extubation since HFJV initiation, comparing conservative (increasing PIP by 1-2 cmH₂O) with progressive strategies (increasing PIP by more than 2 cmH₂O), with analysis restricted to the neonates without congenital heart disease at baseline (sensitivity analysis #5).

(A) Estimated cumulative incidence (95% confidence interval shaded); (B) Estimated cumulative incidence difference (95% confidence interval shaded), using the conservative group as the reference.

Overall Summary

This body of work consists of two target trial emulations using observational database. We focused on studying the effect on early respiratory outcome of 1) early vs. late timing of PDA procedural interventions in preterm infants with hemodynamically significant PDA, and 2) conservative vs. progressive PIP titration strategies in acidotic neonates who initiated HFJV.

In the first study, our analysis suggests that early PDA closure strategy following referral (0–4 days from referral) for a definitive procedure may be associated with short-term respiratory benefit among premature infants with symptomatic PDA, while over a longer-term (45-day) follow-up, there was no difference in the extubation rates based on timing from referral to definitive closure.

In the second study, our findings suggest that, among acidotic neonates initiating HFJV, a progressive PIP titration strategy (i.e., increasing PIP by 3 cmH₂O or more within 1 to 2 hours) may be associated with greater changes in pH and pCO₂ during the first few hours, and potentially earlier extubation, compared to a more conservative strategy (i.e., increasing PIP by 1–2 cmH₂O within 1 to 2 hours), although 95% confidence intervals were compatible with earlier extubation with either strategy.

Discussion and Perspectives

When a RCT is not feasible or practical, EHR data can be applied to emulate a hypothetical target trial that would provide the answer to a causal question. In our studies, we outlined and emulated two target trials, while accounting for the unique aspects of each study.

In the first study, we deal with a “when to start treatment” question, which involves a *grace period*. Because there was no baseline label of treatment assignment in the observational database, a patient’s history can be compatible with both early and late intervention strategies at times in the early grace period (0 to 4 days from referral, as per our protocol).

In the second study, we try to address a “when to start or switch treatment” question. Using observational data, we compared two dynamic treatment strategies, where treatment decisions depended on the progression of time-varying covariates. In our study, pH levels affects the magnitude of PIP titration, and vice versa, which introduces *treatment-confounder feedback*. Traditional methods, however, struggle to account for time-varying confounding in the presence of treatment-confounder feedback.

In both cases, g-methods such as IP weighting can be used to perform the analysis appropriately and account for *grace period* and *treatment-confounder feedback*. In the first study, we describe how we avoided the study design flaws present in previous observational studies that introduced immortal time bias, by introducing a grace period and clearly defining time zero (baseline) that would coincide with time of

eligibility assessment, treatment assignment, and start of follow-up. In the second study, we implemented the emulation of a target trial with EHR data to estimate the comparative effectiveness of PIP management strategies (“conservative” vs. “progressive” strategies) that are sustained over time, accounting for time-varying confounding. However, we acknowledge that neither study provides conclusive evidence to clinical decision-making, mainly due to small sample size, loss to follow-up, and restricted access to potential baseline and post-baseline confounders. In addition, small sample size precluded some clinically important sensitivity analyses.

Despite the aforementioned limitations, our analysis approach can be applied to other similar research questions. Future directions include estimating the same effect via parametric g-formula and examining long-term outcomes, such as the occurrence of bronchopulmonary dysplasia or mortality using a larger dataset.