

Original Article



Comparison of High Versus Low Positive End-Expiratory Pressure in Mechanically Ventilated Patients With Acute Heart Failure: Rationale and Design of the HELP-AHF Trial

Junho Hyun , MD, MSc^{1,*}, In-Cheol Kim , MD, PhD^{2,*}, Ah-ram Kim , MD¹, Hee Jeong Lee , MD, MSc², Sang Eun Lee , MD, PhD¹, Sung-Cheol Yun , PhD³, and Min-Seok Kim , MD, PhD¹

¹Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

²Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea

³Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to

Min-Seok Kim, MD, PhD

Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Email: msk@amc.seoul.kr

*Junho Hyun and In-Cheol Kim contributed equally to this article.

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ABSTRACT

Background and Objectives: Acute decompensated heart failure (ADHF) often necessitates invasive mechanical ventilation (MV) due to respiratory failure. Positive end-expiratory pressure (PEEP) is a critical component in MV management; however, the optimal PEEP level for patients with ADHF remains unclear. The High vErsus Low Positive end-expiratory pressure in mechanically ventilated patients with Acute Heart Failure (HELP-AHF) trial is a multicenter, open-label, randomized controlled study designed to compare the efficacy and safety of high versus low PEEP strategies in this population.

Methods: A total of 120 patients with ADHF requiring MV within 24 hours of initiation will be randomized 1:1 to a high PEEP group (target: 10 cmH₂O) or a low PEEP group (target: 3 cmH₂O).

Results: The primary outcome is ventilator-free days at day 28. Key secondary outcomes include in-hospital mortality, duration of intensive care unit and hospital stay, vasoactive-inotropic support, and rates of heart transplantation or left ventricular assist device implantation. Safety outcomes include hemodynamic instability requiring mechanical circulatory support, pulmonary complications, and weaning-related adverse events.

Conclusions: This HELP-AHF trial aims to provide valuable insights into optimal PEEP strategies in ADHF patients receiving invasive MV. Findings from this study have the potential to inform ventilatory management practices and improve outcomes in this high-risk population.

Trial Registration: ClinicalTrials.gov Identifier: [NCT04853563](https://clinicaltrials.gov/ct2/show/study/NCT04853563)

Keywords: Heart failure; Mechanical ventilation; Positive end-expiratory pressure

INTRODUCTION

Acute decompensated heart failure (ADHF) frequently necessitates supplemental oxygen, and a subset of patients require invasive mechanical ventilation (MV). MV plays a crucial role in alleviating the work of breathing and improving tissue oxygenation in these patients. However, despite the increasing incidence of MV use in cardiac intensive care units,¹⁾ the optimal MV strategy for ADHF remains undefined.

High positive end-expiratory pressure (PEEP) and low tidal volumes are well-established components of ventilatory management in patients with acute respiratory distress syndrome (ARDS).²⁾ Specifically, positive pressure ventilation (PPV) with PEEP prevents atelectasis, enhances oxygenation, and reduces inspiratory effort. However, a recent study on patients with non-ARDS respiratory failure, although it remains unclear whether heart failure (HF) patients were included, reported no significant differences in outcomes between high and low PEEP strategies.³⁾ This uncertainty is further magnified in patients receiving invasive MV primarily for ADHF, where the balance between respiratory and hemodynamic effects is particularly complex.

PPV influences not only gas exchange and lung injury but also cardiac and hemodynamic parameters. In HF, PPV can have a beneficial effect in reducing left ventricular (LV) afterload,⁴⁾ but may also decrease preload, and increase right ventricular (RV) afterload, potentially reducing cardiac output (CO).¹⁾ While non-invasive PPV has demonstrated benefits in patients with acute cardiogenic pulmonary edema, the optimal ventilatory strategy for invasive MV in ADHF remains unclear as a considerable number of patients with ADHF exhibit biventricular failure.⁵⁾ To date, no prospective randomized trial has evaluated the clinical efficacy of high versus low PEEP strategies in patients with ADHF requiring invasive MV. The High vErsus Low Positive end-expiratory pressure in mechanically ventilated patients with Acute Heart Failure (HELP-AHF) trial is a multicenter, open-label, randomized controlled study designed to compare the efficacy and safety of high and low PEEP strategies in this patient population.

METHODS

Trial design and objectives

The HELP-AHF trial is a multicenter, prospective, open-label, randomized controlled trial designed to compare the efficacy and safety of high and low PEEP strategies in patients with ADHF requiring invasive MV (**Figure 1**). Patients are being recruited from two tertiary centers in South Korea: Asan Medical Center (Seoul)

and Keimyung University Dongsan Hospital, (Daegu). Institutional Review Boards at both centers approved the study (Asan Medical Center, AMC-2021-4033), which is being conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The primary objective is to test the hypothesis that a high PEEP strategy improves clinical outcomes compared with a low PEEP strategy.

Randomization and interventions

Eligible patients are randomized 1:1 to high or low PEEP strategies. Management of ADHF follows established guidelines.^{6,7)} Participants receive commonly used ventilator modes, including assist/control ventilation. Potentially correctable etiology of HF is recommended to be corrected as soon as possible in all participants. Tidal volume is adjusted to 6–8 mL/kg predicted body weight, and peak inspiratory pressure is maintained below 30 cmH₂O. Target oxygenation is defined as SpO₂ of 92–96% and PaO₂ of 65–90 mmHg, primarily achieved by adjusting FiO₂ (typically 0.21–0.6). If a higher fraction of FiO₂ is required, the approach is to increase the FiO₂ further rather than adjusting the PEEP. Adjustments to PEEP are considered only when oxygenation remains inadequate despite an FiO₂ of 1.0.

In the low PEEP group, the initial PEEP level is set at 5 cmH₂O and gradually reduced by 1 cmH₂O to achieve a target of 3 cmH₂O, maintaining oxygenation within an FiO₂ range of 0.21–0.60. In the high PEEP group, the initial PEEP level is set at 8 cmH₂O and increased by 1 cmH₂O to a target of 10 cmH₂O.

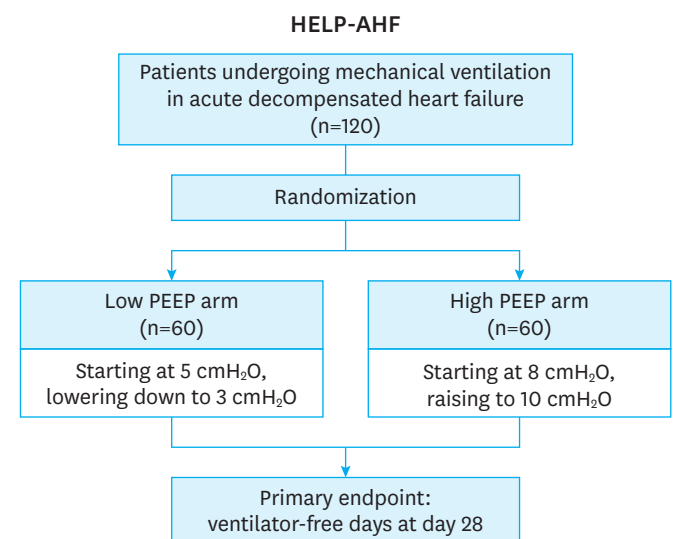


Figure 1. Study flow diagram.

HELP-AHF = High vErsus Low Positive end-expiratory pressure in mechanically ventilated patients with Acute Heart Failure; PEEP = positive end-expiratory pressure.

RESULTS

Study population

Inclusion and exclusion criteria are detailed in **Table 1**. Consecutive patients with ADHF initiating invasive MV are screened for eligibility. Because many patients are sedated, informed consent is obtained from their legal representatives. Inclusion criteria include: adults diagnosed with ADHF as the primary indication for invasive MV initiation who have objective evidence of pulmonary vascular congestion or edema, confirmed by chest radiography and/or ultrasound findings of B-lines suggestive of pulmonary edema. HF was clinically distinguished from other HF-mimicking conditions, such as chronic kidney disease, by identifying structural heart disease on cardiac imaging including evidence of impaired systolic and/or diastolic function. Exclusion criteria were: those on mechanical circulatory support (MCS) at the time of randomization; vasoactive-inotropic score (VIS) >10; severe cardiac valvular abnormalities requiring urgent intervention; evidence of isolated preload-dependent cardiac dysfunction (e.g., isolated RV failure, RV infarction, constrictive pericarditis, cardiac tamponade, or severe pulmonary hypertension without associated LV dysfunction); predominant RV failure (e.g., hepatjugular reflux, Kussmaul's sign, cardiac liver cirrhosis, hepatosplenomegaly, ascites, or thrombocytopenia); suspected or confirmed hypertrophic cardiomyopathy with significant LV outflow tract obstruction; initiation of MV >24 hours prior to randomization; unwitnessed cardiopulmonary resuscitation (CPR) or CPR lasting >30 minutes.

Ventilator weaning

Eligibility of assisted ventilation or MV weaning should be assessed at least twice daily. Inspiratory pressure and FiO₂ levels can be gradually adjusted downward as needed while maintaining the assigned PEEP levels. During pressure supported ventilation, the assigned PEEP protocol is maintained. PEEP may be adjusted during spontaneous breathing trials (SBTs), conducted using a T-piece or minimal MV support (defined as pressure support ≤10 cmH₂O and FiO₂ ≤0.4). Weaning is initiated for patients meeting the following criteria: 1) FiO₂ ≤0.4, 2) responsive and cooperative mental status, 3) adequate cough reflex and coughing power, 4) no significant respiratory acidosis, 5) stable hemodynamics with minimal or no inotropic or vasoactive support, and 6) stable clinical status during SBT, including adequate respiratory rate (5–35 /min) and heart rate (≤140/min or <20% increase from baseline), SpO₂ >90%, and an absence of respiratory distress. After MV weaning, adjunctive oxygen therapy is managed at the discretion of the attending physician. Sedation protocols, thromboprophylaxis, and stress ulcer prophylaxis follow current guidelines.⁷⁻⁹⁾

Study endpoints

The primary endpoint is the mean difference in ventilator-free days and alive at day 28. Non-survivors within 28 days from randomization are assigned 0 ventilator-free day, regardless of prior weaning success. Key secondary endpoints include in-hospital mortality, length of ICU and hospital stays, VIS, duration of inotropic and/or vasoactive agent use, and rates of heart transplantation or LV assist device implantation (**Table 2**). Safety endpoints

Table 1. Inclusion and exclusion criteria

Criteria
Inclusion criteria
1. Patient who is diagnosed with ADHF requiring invasive MV and objective evidence of pulmonary vascular congestion and/or edema and elevated natriuretic peptide <ul style="list-style-type: none"> A. Objective evidence of pulmonary congestion or edema judged by either of the following tests: simple chest radiography, B-lines by lung ultrasound suggestive of pulmonary edema B. Elevated natriuretic peptides defined by either BNP ≥100 pg/mL or NT-proBNP ≥300 pg/mL
2. Age ≥19 years
Exclusion criteria
1. Mechanical circulatory support or vasoactive inotropic score of more than 10 at the time of randomization
2. Cardiac valvular abnormalities necessitating emergent or urgent valvular intervention
3. Isolated preload-dependent cardiac failure <ul style="list-style-type: none"> Isolated RV failure, RV infarction, constrictive pericarditis, cardiac tamponade, severe pulmonary hypertension without LV dysfunction
4. Clinical evidence of predominant RV failure judged by attending physician's discretion
5. Invasive MV initiated 24 hours or more at the time of randomization
6. Unwitnessed CPR or witnessed CPR lasting more than 30 minutes
7. Prior or current diagnosis of hypertrophic cardiomyopathy with significant LVOT obstruction
8. Severe neurologic abnormalities or pre-existing impaired consciousness at the time of randomization <ul style="list-style-type: none"> A. Hemorrhagic or ischemic stroke B. Pre-existing impaired consciousness that cannot perform adequate coughing and/or need frequent suction to maintain airway patency
9. Pregnant or lactating women
10. Life expectancy less than a year

ADHF = acute decompensated heart failure; MV = mechanical ventilation; BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RV = right ventricle; LV = left ventricle; CPR = cardiopulmonary resuscitation; LVOT = left ventricular outflow tract.

Table 2. Primary and secondary clinical endpoints

Endpoints
Primary endpoint
Ventilator-free days and alive at day 28
Secondary endpoints
1. In hospital mortality
2. Mortality at 28- and 90-days
3. Rescue MCS therapy due to hemodynamic instability
4. Vasoactive-inotropic score
5. Days on inotropic or vasoactive agents
6. Days on intravenous sedative agents
7. Rates of heart transplantation, left ventricular assist device implantation
8. Length of intensive care unit and hospital stay
Safety endpoints
1. In-hospital mortality
2. Pulmonary complications
A. Pneumothorax
B. Ventilator-associated pneumonia
C. Severe hypoxemia
D. Atelectasis requiring bronchoscopic toileting
3. Weaning failure
A. Failure to pass spontaneous breathing trial
B. Re-intubation within 48 hours after extubation
4. Rate of tracheostomy
5. Refractory shock requiring CPR and/or MCS
6. Rates of heart transplantation, left ventricular assist device implantation

MCS = mechanical circulatory support; CPR = cardiopulmonary resuscitation.

include in-hospital mortality, hemodynamic complications, and pulmonary complications. Hemodynamic complications are defined as requiring MCS for rescue therapy due to hemodynamic instability. Pulmonary complications include ventilator-associated pneumonia, pneumothorax, severe atelectasis requiring bronchoscopic toileting, or severe hypoxemia ($\text{PaO}_2 < 55$ mmHg on $\text{FiO}_2 > 0.6$, requiring increased PEEP above the protocol-specified level). Weaning-related adverse events include weaning failure or performing tracheostomy. Weaning failure is defined as the failure to pass a SBT or reintubation within 48 hours post-extubation. Tracheostomy is advised based on current guidelines when prolonged MV, difficulty in secretion management, or impaired consciousness preclude timely extubation.¹⁰⁾ The decision is left to the discretion of the attending physician.

Sample size calculation and statistical analysis

No previous randomized or large-scale prospective observational trials have evaluated the duration of invasive MV in ADHF patients over 28 days. Therefore, the study is a pilot design and primary finding would be exploratory. However, the rationale for determining the study sample size was based on the findings from a prospective registry of mechanically ventilated patients with congestive HF demonstrating a mean number of 19.9 ± 6.4 ventilator-free days over 28 days.¹¹⁾ With an alpha significance level of 0.05 and 85% power, accounting for 5% crossover and drop-out rates, a total sample size of 120 patients (60 per group) is

required to detect an 18% increase in the mean ventilator-free days, equivalent to a 3.6-day improvement. This would be acceptable significant difference.

Endpoint analyses are conducted according to the intention-to-treat principle. Difference of the number of ventilator-free days at day 28 are assessed using the Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Differences in categorical variables between the two groups are compared using the χ^2 or Fisher's exact test, as appropriate. Cumulative time-to-event outcomes for liberation from MV and in-hospital mortality are presented using Kaplan-Meier curves and compared using the log-rank test. All p values are two-sided, and a p value < 0.05 is regarded as statistically significant. All analyses are conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA).

Safety monitoring

Safety endpoints are listed in **Table 2**. Interim analyses will be conducted at 50% and 70% enrollment. An independent Data Safety Monitoring Board will review safety data and recommend whether to continue or terminate the trial.

DISCUSSION

MV is a life-saving therapy for patients with ADHF experiencing acute respiratory failure due to cardiogenic pulmonary edema. Although hemodynamic stabilization and decongestive therapies can facilitate ventilator weaning, some patients require prolonged MV, which is associated with worse in-hospital outcomes.¹²⁾

In cases of acute respiratory failure caused by ADHF, PPV reduces respiratory effort, decreases the work of breathing, and improves oxygenation. Beyond its ventilatory benefits, PPV induces notable hemodynamic effects. Increased pleural pressure decreases RV venous return from extrathoracic veins, while increased transpulmonary pressure, defined as the difference between alveolar and pleural pressure, raises pulmonary vascular resistance, thereby reducing RV output. Studies have reported that reduced RV filling pressure due to PPV leads to decreased CO.^{13,14)} RV stroke volume is particularly sensitive to afterload because of its unique myocardial mass and geometry.¹⁵⁾ Consequently, PPV can have detrimental effects in cases of RV-dominant failure.

Conversely, PPV exerts favorable effects on LV failure. Increased pleural pressure elevates both LV and aortic pressures,¹⁾ decreases systemic vascular resistance via aortic baroreceptor reflex, and increases the pressure differential between intra- and extrathoracic

organs,¹⁶⁾ leading to reduced LV transmural pressure.¹⁷⁾ These changes alleviate LV loading conditions. Additionally, elevated transpulmonary pressure decreases LV preload, benefitting patients with elevated LV filling pressure.⁴⁾ Thus, PPV generally has a net positive hemodynamic impact in LV failure.¹⁸⁾

Considering opposing effects of PPV on the LV and RV, it is difficult to determine target PEEP level in ADHF patients who frequently have biventricular dysfunction. Furthermore, few studies have demonstrated the beneficial effect of PPV on clinical outcomes beyond hemodynamic improvements. PPV through non-invasive ventilation for acute cardiogenic pulmonary edema has been shown to reduce intubation risk and rapidly improve symptoms,^{19,20)} with potential mortality benefits.²¹⁾ However, no randomized study has directly compared the efficacy of different PEEP levels in ADHF patients requiring invasive MV.

The HELP-AHF trial design addresses several challenges. First, PEEP can exert contrasting hemodynamic effects on preload- and afterload-dependent conditions, necessitating the selection of appropriate candidates to ensure safety and efficacy. Hemodynamic compromise from high PEEP may require extracorporeal membrane oxygenation, potentially attenuating its differential effects. Therefore, patients with overt RV failure or significantly elevated VIS are excluded to mitigate safety concerns. Second, while high PEEP can lead to alveolar overdistention and volutrauma, low PEEP increases the risk of atelectrauma. The low PEEP group targets a physiologic level of 3–5 cmH₂O,²²⁾ while the high PEEP group targets 8–10 cmH₂O, based on evidence that PEEP of up to 12 cmH₂O improves CO, whereas PEEP ≥16 cmH₂O reduces CO.¹⁴⁾ Studies have also reported hemodynamic benefits at 10 cmH₂O in acute myocardial infarction and cardiogenic shock.¹⁸⁾

Despite its strengths, the design of this study has several limitations. First, individualized PEEP tailored to the hemodynamic profile of each patient is not implemented. Previous research has shown that the optimal PEEP level for hemodynamic response varies with pulmonary capillary wedge pressure.⁴⁾ Second, the study does not include monitoring of hemodynamic responses to different PEEP levels, which could provide insights into clinical outcomes. Incorporating such monitoring would require pulmonary artery catheterization, potentially limiting patient enrollment. Third, the primary outcome of ventilator-free days, although widely used in recent randomization trials,^{3,23)} is an indirect measure of clinical practice. However, it remains closely associated with adverse in-hospital outcomes.¹²⁾

To date, no randomized trial has evaluated the comparative efficacy of high versus low PEEP levels in ADHF patients initiating

invasive MV. The HELP-AHF trial, an investigator-initiated, multicenter, open-label, randomized study, aims to determine the optimal PEEP strategy for this population. Its findings are expected to provide critical insights for improving the management of invasive MV in patients with ADHF.

ORCID iDs

Junho Hyun 
<https://orcid.org/0000-0003-4211-3081>
 In-Cheol Kim 
<https://orcid.org/0000-0002-5751-2328>
 Ah-ram Kim 
<https://orcid.org/0000-0003-2489-948X>
 Hee Jeong Lee 
<https://orcid.org/0000-0002-0243-6954>
 Sang Eun Lee 
<https://orcid.org/0000-0002-7290-2463>
 Sung-Cheol Yun 
<https://orcid.org/0000-0001-8503-109X>
 Min-Seok Kim 
<https://orcid.org/0000-0003-0860-3650>

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Conflict of Interest

The authors have no financial conflicts of interest.

Trial Registration

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Author Contributions

Conceptualization: Hyun J, Kim MS; Formal analysis: Hyun J; Funding acquisition: Kim MS; Investigation: Hyun J, Kim IC, Kim AR, Lee HJ, Lee SE, Kim MS; Methodology: Hyun J, Yun SC, Kim MS; Project administration: Hyun J, Kim MS; Resources: Kim MS; Supervision: Hyun J, Kim IC, Kim AR, Yun SC, Kim MS; Visualization: Hyun J; Writing - original draft: Hyun J, Kim MS; Writing - review & editing: Hyun J, Yun SC, Kim MS.

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