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RESEARCH ARTICLE

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Efficacy and safety of a 72-h infusion of prostacyclin (1 ng/kg/min) in mechanically ventilated patients with pulmonary infection and endotheliopathy—protocol for the multicenter randomized, placebo-controlled, blinded, investigator-initiated COMBAT-ARF trial

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Abstract

Background: Acute respiratory failure (ARF) is common in critically ill patients, and 50% of patients in intensive care units require mechanical ventilation [3, 4]. The COVID-19 pandemic revealed that COVID-19 infection induced ARF caused by damage to the microvascular pulmonary endothelium. In a randomized clinical trial, mechanically ventilated COVID-19 patients with severe endotheliopathy, as defined by soluble thrombomodulin (sTM) ≥ 4 ng/mL, were randomized to evaluate the effect of a 72-h infusion of low-dose prostacyclin 1 ng/kg/min or placebo. Twenty-eight-day mortality was 21.9% versus 43.6% in the prostacyclin and the placebo groups, respectively (RR 0.50; CI 0.24 to 0.96 $p = .06$). The aim of the current trial is to investigate if this beneficial effect and safety of prostacyclin also are present in any patient with suspected pulmonary infection requiring mechanical ventilation and concomitant severe endotheliopathy.

Materials and Methods: This is a multi-center, randomized, blinded, clinical investigator-initiated phase 3 trial in mechanically ventilated patients with suspected pulmonary infection and severe endotheliopathy, as defined by sTM ≥4 ng/mL. Patients are randomized 1:1 to a 72-h infusion of low-dose prostacyclin (iloprost) 1 ng/kg/min or placebo (an equal volume of saline). Four-hundred fifty patients will be included.

The primary endpoint is 28-day all-cause mortality. Secondary endpoints include 90-day mortality, days alive without vasopressor, mechanical ventilation, and renal replacement therapy in the ICU within 28 and 90 days, and the number of serious adverse reactions or serious adverse events within the first 7 days.

Discussion: This trial will investigate the efficacy and safety of prostacyclin vs. placebo for 72-hours in mechanically ventilated patients with any suspected pulmonary infection and severe endotheliopathy, as defined by sTM ≥4 ng/mL. Trial endpoints focus on the potential effect of prostacyclin to reduce 28-day all-cause mortality.

KEYWORDS

acute respiratory failure, clinical trial, infectious pulmonary endotheliopathy, mechanical ventilation, prostacyclin, thrombomodulin

1 | INTRODUCTION

The COVID-19 pandemic highlighted the detrimental consequences of acute respiratory failure (ARF) on patient morbidity and mortality.[1,2] ARF is common in critically ill patients, and more than 50% of all intensive care unit (ICU) patients require mechanical ventilation.[3,4] ARF occurs in a heterogenous patient group, most often in the setting of pneumonia, sepsis, severe trauma, and following major surgery.[5–7] Despite improvements in intensive care capabilities, ARF mortality remains high, and the only treatment option, to date, is antibiotics and supportive care.[8] A recent Cochrane analysis found no evidence for that any drug was effective in reducing deaths in mechanically ventilated patients with ARF, hence highlighting the high unmet medical need.[9]

The COVID-19 pandemic revealed that infection-induced ARF is caused by damage to the microvascular pulmonary endothelium.[10] The endothelium is a single-cell layer that lines the innermost part of all vessels throughout the body.[11] The endothelium maintains the delicate balance between the circulating blood and the underlying tissues, and this interface maintains immunity and blood fluidity, and transfers water and nutrients.[11] The damage to the pulmonary endothelium compromises the oxygen delivery from the pulmonary alveoli to the circulating blood.[12] Inadequate oxygenation of the blood (hypoxemia) can lead to organ failure, including the heart, kidneys, liver, and the brain, collectively entitled multiorgan failure (MOF). Thrombomodulin is a key member of the anticoagulant protein C system, and its cleavage from the endothelial surface contributes to the prothrombotic phenotype observed in mechanically ventilated COVID-19 patients with damage to the endothelium, here entitled as endotheliopathy.[13,14] More specifically, we have reported that the level of circulating soluble thrombomodulin (sTM), which is a marker of endothelial damage, is strongly associated with organ failure and mortality in patients with systemic infections.[15] Regarding COVID-19-infected patients, Goshua and colleagues reported that those with endotheliopathy, defined by a sTM level above 4 ng/mL, reflecting severe endotheliopathy, had significantly increased mortality (40% vs. 20%) compared to those patients with sTM levels below 4 ng/mL.[16] We have recently extended these findings beyond COVID-19 infection by studying 349 mechanically ventilated patients in a general intensive care setting.[17]

Prostacyclin is an endogenous prostanoid formed and released by endothelial cells, with paracrine function including vasodilation and platelet inhibition. Because of these properties, it was introduced as a pharmacological therapy in 1979 for patients with primary pulmonary hypertension and critical limb ischemia in high doses.

In the new millennium, it was reported that prostacyclin also confers potent endothelial cytoprotection by: synthesizing endothelial glycocalyx constituents (hyaluronic acid),[18,19] acting on prostaglandin I (IP_1) receptors on endothelial progenitor cells, leading to re-endothelium-formation in damaged vessels,[20] upregulating VE-cadherin responsible for tight-junction integrity, i.e., preventing capillary leakage,[21] inducing peroxisome PPAR attenuation of NF-kB and TNF activation in ischemia–reperfusion injury, which minimizes the inflammatory hit on the endothelium,[22] and protecting against ischemia–reperfusion injury through the PGI_2-PPARα-HEME Oxygenase-1 signaling pathway that provides robust rejuvenation of the damaged endothelium.[23] In 2010, the outcome of critically ill patients needing renal replacement therapy was studied at ICU 4131 at Rigshospitalet. We found that those patients receiving prostacyclin as an anticoagulant during renal replacement therapy displayed a substantially lower 30-day mortality than patients receiving heparin (21% vs. 39%), despite being more critically ill.[24] We speculated that this may be due to a spill-over effect of prostacyclin to the systemic circulation.

In a study in healthy volunteers, we demonstrated that low-dose prostacyclin (Iloprost) did not adversely affect blood pressure or platelet function but instead appeared to improve endothelial function, as evaluated by sTM [EudraCT no: 2011-006200-12]. The effect of low-dose prostacyclin infusion (1 ng/kg/min) was, therefore, investigated in two randomized, double-blind pilot studies in major surgery ($n = 56$)[25] and in septic shock patients ($n = 18$).[26] These trials documented no adverse effects on blood pressure or platelet function. On the contrary, prostacyclin significantly improved endothelial function and integrity, as measured by validated biomarkers, in all groups. In septic shock patients, we also found that the sequential organ failure assessment (SOFA) score was significantly reduced together with reduced duration of mechanical ventilation. In addition, a lower 30-day and 90-day mortality (8% vs. 34%; 25% vs. 50%) was demonstrated.[26]

In the COMBAT COVID-19 trial, we introduced a precision medicine approach by using the biomarker sTM at a level above 4 ng/mL as an inclusion criterion to ensure that only mechanically ventilated patients with severe endotheliopathy and high predicted mortality were included.[27] Eighty mechanically ventilated COVID-19 patients were randomized to a 72-h prostacyclin (1 ng/kg/min) infusion vs. placebo (NCT04420741). The primary endpoint was the median number of days alive without mechanical ventilation at 28 days, which was 16 days in the prostacyclin group vs. 5 days in the placebo group (difference of the medians: 11 days [95% CI −5–21], $p = .07$). The secondary endpoints included 28-day mortality, which was 21.9% versus 43.6% in the prostacyclin and the placebo groups, respectively (RR 0.50 95% CI 0.24–0.96; $p = .06$). The incidence of serious adverse events (SAEs) <7 days was 2.4% vs. 12.8% (RR 0.19 [95% CI 0.001–1.11], $p = .10$) in the prostacyclin and the placebo groups, respectively.

Recently, we reported the results of COMBAT-SHINE, a randomized clinical trial in patients with septic shock and severe endotheliopathy, identified by sTM >10 ng/mL, who received either prostacyclin 1 ng/kg/ min or placebo.[28] The trial was stopped for futility after the inclusion of 278 patients, concluding that the administration of prostacyclin would be unlikely to improve outcomes in sepsis patients.

1.1 | Trial hypothesis

Prostacyclin may be beneficial as an endothelial rescue treatment, as it is anticipated to deactivate the endothelium and restore vascular integrity in mechanically ventilated patients with infectious pulmonary endotheliopathy, ultimately improving survival.

2 | MATERIALS AND METHODS

2.1 | Trial design

This is a multicenter, randomized (1:1, prostacyclin: placebo), placebo-controlled, blinded, investigator-initiated trial in mechanically ventilated patients with suspected pulmonary infection and endotheliopathy, as defined by circulating TM ≥4 ng/mL at the time of inclusion, investigating the efficacy and safety of continuous intravenous administrating of prostacyclin (1 ng/kg/min) versus placebo for 72 h, in a total of 450 patients. For definitions concerning the project, see Appendix S1, and for the full study protocol, see Appendix S2.

An independent Data Safety Monitoring Board (DSMB) will assess safety every for 100 patients included. The DSMB will review 28-day mortality and other safety endpoints.

2.2 | Trial registration

EudraCT no 2022-004079-17 and VMK-2301624. The study is monitored by the Capital Region GCP Unit, Bispebjerg Hospital, Copenhagen, Denmark.

2.3 | Setting

The trial will be conducted at the ICU's at Copenhagen University Hospital—Herlev and Gentofte, Copenhagen University Hospital—Bispebjerg—and Frederiksberg, Copenhagen University Hospital—North Zealand, and at Zealand University Hospital—Køge.

2.4 | Study population

2.4.1 | Inclusion criteria

Patients will be included in the COMBAT-ARF trial if they fulfil the following criteria:

1. Adult intensive care patients (age ≥ 18 years)
   AND
2. Suspected pulmonary infection
   AND
3. Need for mechanical ventilation (< 24 h from time of screening)
   AND
4. sTM ≥4 ng/mL

2.4.2 | Exclusion criteria

Patients are not eligible for inclusion in this trial if they fulfil one or more of the following criteria:

1. Withdrawal from active therapy.
2. Pregnancy (non-pregnancy confirmed by the patient having a negative urine- or plasma hCG or being postmenopausal, defined as females at 60 years old or beyond or at the investigators discretion).
3. Septic shock according to the Sepsis 3 criteria AND sTM >10 ng/mL.
4. Known hypersensitivity to iloprost or to any of the other contents.
5. Previously included in this trial or other prostacyclin trials within 30 days.
6. Life-threatening bleeding, defined by the treating physician.
7. Known severe heart failure (NYHA class IV).
8. Suspected acute coronary syndrome.

Patients enrolled in other interventional trials will not be excluded unless the protocols of the two trials collide. A co-enrolment agreement will be established between the sponsors.

2.5 | Screening

It will be the responsibility of the treating physician to identify eligible adult mechanically ventilated patients with severe endotheliopathy due to a suspected respiratory infection and pass on information to the trial. All patients that fulfil the inclusion criteria (as described in section 8.1,

bullet 1–3) are subjected to screening, which will be recorded in the screening log. Patients fulfilling any of the exclusion criteria will not participate. The reasons for not entering the trial will be registered. The distribution of screened patients will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram.[29]

2.6 | Randomisation

The sponsor is responsible for setting up the randomisation system. The randomisation sequence will be done in permuted blocks of variable sizes stratified for trial site using centralized, concealed allocation. The randomisation sequence will be generated 1:1 (active/placebo) using the online randomisation software 'Sealed Envelope' (https://www.sealedenvelope.com/). Once generated, the randomisation sequence will be formatted and uploaded into REDCap to facilitate centralized, web-based allocation according to local written instruction. The randomisation sequence will be printed and signed by two independent individuals and stored in a sealed envelope in sponsors TMF. The patient randomisation at each site will be done in the electronic system REDCap, where each patient will be given a unique randomisation number/Trial ID number. The randomization sequence will be concealed from all clinicians, patients, investigators and statisticians and will first be opened after completion of all trial related procedures, and statistically analyses are finalized.

2.7 | Trial intervention

A 1:1 randomized stratification for active study drug or placebo infusion for 72 h is used. A total of 450 patients will be treated in accordance with state-of-the-art therapy. Interventions are considered emergency procedures, and study drug infusion should be commenced as soon as possible after screening and randomization. Patients with active treatment ($N = 225$ patients) will receive a low-dose prostacyclin infusion 1.0 ng/kg/min, whilst the placebo group ($N = 225$ patients) receives a saline infusion, both for 72 h. Patients in the trial will otherwise be treated according to the standard of care, with no other difference between the two groups besides of the active or placebo intervention. This dosing regimen was chosen since intravenous doses of prostacyclin 0.5–2.0 ng/kg/min have been reported to be successful at achieving endothelial modulating/preserving effect with no significant hemodynamic or platelet aggregation complications.[25–27]

2.8 | Outcome measures

2.8.1 | Primary outcome measure

28-day all-cause mortality.

2.8.2 | Secondary outcome measures

- 90-day all-cause mortality.
- Days alive without vasopressor in the ICU within 28 and 90 days.
- Days alive without mechanical ventilation in the ICU within 28 and 90 days.
- Days alive without renal replacement in the ICU within 28 and 90 days.
- Number of patients with one or more serious adverse reactions (SAR) within the first day 7.
- Number of patients with one or more serious adverse event (SAE) within the first day 7.

2.9 | Blinding

To circumvent selection bias, researchers and health care personnel will be blinded to the treatment assignment. Furthermore, to avoid investigator, health care personnel, and patient performance and detection bias, patients will be randomized to receive either prostacyclin (Ilomedin®, Bayer AG, Leverkusen, Germany) or a placebo indistinguishable in color, consistency, and volume. Blinded study and non-study personnel will record clinical data and analyze blood samples. All randomized patients that have received prostacyclin will continue to be included in the assessments of its safety and efficacy. Also, all analyses of the endpoints are performed by blinded personnel. We expect no loss to follow-up due to the unique Danish identification number.

2.10 | Data registration and monitoring

Data will be entered into a central web-based electronic case report form (eCRF) using the data management system REDCap® software (REDCap 8.10.18—© 2019 Vanderbilt University). The eCRF is password-protected, audit-trailed, encrypted that allows for detailed centralized and de-centralized surveillance of data completeness overall and at each site. Each participating trial site will only have access to their own data.

2.11 | Serious adverse reactions and serious adverse events

Safety assessment will be done by comparing safety events for prostacyclin versus placebo. All SAEs will be captured as part of the daily routine in the patient electronic health record (i.e., ICU notes, laboratory reports) and this will allow for later inspection if needed. The investigator will record the occurrence of all SARs and those SAEs of special interest until day 7 for all included patients in the electronic CRF. After day 7, no further safety concerns are expected due to the short half-life of the trial drug. Safety assessment will be done comparing safety events for prostacyclin versus placebo.

Patients will not be withdrawn from the trial if a SAR occurs. For a detailed description of known SARs (as well as adverse reaction) for Ilomedin, see section 4.8 in the Danish SmPC. The volume of

72 mL NaCl per 24 h does not gives any safety concerns in this population.

2.11.1 | SAEs of special interest

The following events are events of special interest, as they either are relevant due to the pharmacokinetic of Ilomedin or of special concern in these patients, as identified in the SmPC for Iloprost:

- Ischemic events (Cerebral (verified by CT), ST Elevation Myocardial Infarction (STEMI) and Non-STEMI, intestinal or limb ischemia) [32].
- Bleeding events requiring more than 4 RBCs within 24 h or ongoing bleeding.
- Bleeding events (intracerebral hemorrhage (verified by CT) and lower gastrointestinal bleeding (defined as bloody diarrhea and rectal bleeding)).
- Severe cardiac failure (defined as severe cardiogenic shock and ejection fraction <20% cardiac ultrasound).
- Pulmonary embolism (symptomatic and verified by CT).
- Deep vein thrombosis (symptomatic and verified by ultrasound).

Only events that fulfilled the serious criteria will be recorded. These SAEs are not subject to expedited reporting by the site to the sponsor but must be recorded in the electronic CRF immediately after day 7, so that the sponsor at any time has the possibility to monitor the occurrence of these SAEs and make a benefit/risks assessment of the trial.

2.12 | Approval

The trial is approved by the Danish Medicines Agency (EudraCT no. 2022-004079-17), the Committees on Health Research Ethics in the Capital Region of Denmark (VMK-2301624), and the Danish Data Protection Agency. All patients will be enrolled after consent from a scientific guardian who is independent of the trial.

To make clinical trials with the goal of improving the treatment of critical ill patients, the treatment has to be initiated as early as possible where patients are temporarily incompetent. Therefore, informed consent is obtained after the inclusion of the patient.

The investigator or his/her qualified designee must as soon as possible after the inclusion of the patient obtain written consent from the patient itself or proxy consent from both a scientific guardian and next-of-kin. Patients, who, during the course of this trial, become able to give consent, will be asked to participate and give their consent, even though a proxy consent is obtained.

2.13 | Statistics

Descriptive statistics will be calculated for all endpoints. All summary statistics of continuous variables will include n, mean, standard deviation, median, min/max, and inter quartile ranges. All summary statistics of frequency tables will include counts and percentages. *p*-values <.05 for the primary endpoint are considered significant.

Twenty-eight-day all-cause mortality will be compared in the ITT population using Fisher's exact test, and effect size expressed as risk ratios with confidence intervals. All-cause mortality will be further illustrated using Kaplan–Meier curves. Ninety-day mortality will be compared in the ITT population using Fisher's exact test, and effect size expressed as risk ratios with confidence intervals and further illustrated using Kaplan–Meier curves. Other secondary endpoints will be compared using the Wilcoxon test, and differences expressed as changes in medians with non-parametric-based bootstrapped 95% confidence interval.

2.13.1 | Sample size estimation

Patients will be recruited in a 1:1 ratio (Prostacyclin:Placebo). The number of patients participating is based on a sample size calculation using the 28-day mortality data in mechanically ventilated COVID-19 patients with sTM >4 ng/mL from a randomized, double-blind, placebo-controlled clinical trial (NTC 04420741) showing a 50% reduction in the prostacyclin arm.[27] Assuming, conservatively, a 30% relative risk reduction in mortality in the prostacyclin arm (from 39% to 26%%) and providing the trial with 80% power to detect this difference at a significance level of 0.05, this will require 203 patients per arm and 406 patients in total. To allow for a 10% drop out, 450 patients will be included. The statistical analysis plan will be published before the last patient is included in the trial, and the analysis of the blinded data from the randomized trial will be performed by Prof. Theis Lange, Section of Biostatistics, Department of Public Health, University of Copenhagen.

2.14 | Populations and sub-groups

The definitions of trial populations are as follows:

Intention-to-treat	This will comprise all randomized patients (except those randomized in error) This population will be evaluated for all endpoints
Per-protocol	This is a subset of the intention-to-treat population encompassing correctly included patients who have received prostacyclin or placebo according to the protocol (i.e., 72-h infusion of prostacyclin or placebo after inclusion or until dead or discharged to ward, whichever comes first). This population will be evaluated for the primary endpoint only

No sub-group analyses are planned. The number of patients in and the available data for the populations will be described in the required reports to the Danish Medicines Agency and Ethics Committee, and in peer-reviewed scientific papers.

2.15 | Trial organization and management

The COMBAT-ARF trial is performed at the ICU's at the Copenhagen University Hospitals—Herlev Hospital, Bispebjerg and Frederiksberg Hospital and North Zealand Hospital and at Zealand University Hospital—Køge together with the CAG Center for Endotheliomics and the Department of Clinical Immunology, Copenhagen University Hospital—Rigshospitalet. The Management Committee encompass the Principal Investigator, Dr. P Søe-Jensen, Copenhagen University Hospital–Herlev and Gentofte, and the other local Investigators and Prof. Johansson, Chair at CAG Center for Endotheliomics. This group is responsible for the overall management and coordination of the trial. Site investigators will manage and coordinate the trial at the sites. The principal investigator is responsible for data collection and maintenance of trial documents. Co-enrolment of participants in other interventional trials have to be approved by the COMBAT-ARF management committee but is generally appreciated.

2.16 | Data sharing

The trial results will be published in a peer-reviewed open source international clinical journal. De-identified data will be made publicly available 12 months after the 1-year follow-up of the last randomized patient, according to the ICMJE recommendations.

3 | DISCUSSION

3.1 | Intervention

The COVID-19 pandemic highlighted the detrimental consequences of acute respiratory failure (ARF) on patient morbidity and mortality.[1,2] It was further revealed that this was caused by injuries to the microvascular pulmonary endothelium, resulting in a pro-thrombotic phenotype secondary to the shedding of thrombomodulin from the endothelial surface, ultimately leading to the shut-down of the protein C system.[10,13,15,16]

The COMBAT COVID-19 trial showed that treating mechanically ventilated COVID-19 patients and concomitant endotheliopathy with low-dose prostacyclin reduced 28-day mortality from 43.6% to 21.9%, respectively (RR% CI 0.24–0.96, [$p = .06$]).

The results described above are the rationale for the current trial to investigate if prostacyclin infusion is also beneficial for mechanically ventilated patients with suspected pulmonary infection of any origin and severe endotheliopathy.

3.2 | Outcome

The primary endpoint in the present trial will be 28-day all-cause mortality. This builds on the results of the COMBAT COVID-19 trial, where an intervention with prostacyclin 1 ng/kg/in for 72 h appeared beneficial for survival in mechanically ventilated COVID-19 patients with severe endotheliopathy, as evaluated by sTM ≥4 ng/mL, although this was not the primary outcome.

3.3 | Strengths

The trial is conducted with a stringent methodology, which complies with international guidelines for clinical trials and good clinical practice. The trial design includes concealed group allocation, blinding to the patient, clinical staff, the investigators, the outcome assessors, and the trial statistician. The trial is GCP-monitored. Sample size estimations and trial design are based on the currently best evidence.

3.4 | Limitations

The development of acute respiratory failure is a multicellular event where cells in the circulating blood, the endothelium, and the cells of the lungs are involved. The current trial is limited in its scope to investigate the potential role of the endothelial cell in the process when acute respiratory failure is established and, hence, the current trial can only assess the potential effect of prostacyclin for this purpose. The current trial is also confined to a limited number of Danish intensive care units.

4 | PERSPECTIVE

Being a phase 3 trial and using mortality as the primary endpoint ensures both that the correct number of patients are included and that the results become rapidly available to the scientific and regulatory communities, with the perspective to ensure the clinical implication of the trial.

5 | TRIAL STATUS

The trial is currently recruiting at 4 active trial sites. Patient inclusion was initiated on 15 April 2024, and the trial is expected to end in 2026.

AUTHOR CONTRIBUTIONS

The manuscript was written by Pär I Johansson, and all authors reviewed and approved the final version.

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Finances: The research project is investigator initiated, and the respective hospitals involved in the trial also support the project with personnel and laboratory facilities.

Neither patients nor health personnel will receive any remuneration from participating in the trial. The Novo Nordisk Foundation and the Benzon Foundation have no influence on the design, the conduct, or the results of the trial. Pär I Johansson is a co-inventor of a patent covering the use of sTM to identify critically ill patients with severe endotheliopathy and to treat these with low-dose prostacyclin. All others declare that they have no competing interests.

FUNDING INFORMATION

The trial sponsor, Pär I. Johansson, has received unrestricted research grants of 7 million DKK from the Novo Nordisk Foundation and 4.1 million DKK from the Benzon Foundation. The amount is paid to and administered by Rigshospitalet, Copenhagen University Hospital, and administered from there.

DATA AVAILABILITY STATEMENT

The trial results will be published in a peer-reviewed open source international clinical journal. De-identified data will be made publicly available 12 months after 1-year follow-up of the last randomised patient according to the ICMJE recommendations.

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REFERENCES

1. Marini JJ, Gattioni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323:2329-2330.
2. Bos LDJ, Sjoding M, Sinha P, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts. *Lancet Respir Med*. 2021;9:1377-1386.
3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315:788-800.
4. Kempker JA, Abril MK, Chen Y, Kramer MR, Waller LA, Martin GS. The epidemiology of respiratory failure in the United States 2002–2017: a serial cross-sectional study. *Crit Care Explor*. 2020;2:e0128.
5. Eworuke E, Major JM, Gilbert McClain LI. National incidence rates for acute respiratory distress syndrome (ARDS) and ARDS cause-specific factors in the United States (2006–2014). *J Crit Care*. 2018;47:192-197.
6. Danish Intensive Care Database - Annual report 2019/2020 - Final version april 2021 7.
7. Confalonieri M, Salton F, Fabiano F. Acute respiratory distress syndrome. *Eur Respir Rev*. 2017;26:160116.
8. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nature Rev*. 2019;5:18.
9. Lewis SR, Pritchard MW, Thomas CM, Smith AF, Cochrane Emergency and Critical Care Group. Pharmacological agents for adults with acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2019;7:CD004477.
10. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128.
11. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood*. 2003;101:3765-3777.
12. Teuwen L, Geldhof V. Pasut a et al COVID-19: the vasculature unleashed. *Nat Rev Immunol*. 2020;20:389-391.
13. Loghmani H, Conway EM. Exploring traditional and nontraditional roles for thrombomodulin. *Blood*. 2018;132:148-158.
14. Pfortomueller CA, Spinetti T, Urman RD, et al. COVID-19-associated acute respiratory distress syndrome (CARDS): current knowledge on pathophysiology and ICU treatment—a narrative review. *Best Pract Res Clin Anaesthesiol*. 2021;35:351-368.
15. Johansen ME, Johansson PI, Ostrowski SR, et al. Profound endothelial damage predicts impending organ failure and death in sepsis. *Semin Thromb Hemost*. 2015;41:16-25.
16. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol*. 2020;7:e575-e582.
17. Schønemann-Lund M, Itenov TS, Larsson JE, Lindegaard B, Johansson PI, Bestle MH. Endotheliopathy is associated with slower liberation from mechanical ventilation: a cohort study. *Crit Care*. 2022;26:33.
18. Bruggeman LA, Pellicoro JA, Horigan EA, Klotman PE. Thromboxane and prostacyclin differentially regulate murine extracellular matrix gene expression. *Kidney Int*. 1993;43:1219-1225.
19. Sussmann M, Sarbia M, Meyer-Kircrath J, et al. Induction of hyaluronic acid synthase 2 (HAS2) in human vascular smooth muscle cells by vasodilatory prostaglandins. *Circ Res*. 2004;94:592-600.
20. Birukova AA, Tian Y, Dubrovskyi O, et al. VE-cadherin trans-interactions modulate Rac activation and enhancement of lung endothelial barrier by iloprost. *J Cell Physiol*. 2012;227:3405-3416.
21. Kawabe J, Yuhki K, Okada M, et al. Prostaglandin I2 promotes recruitment of endothelial progenitor cells and limits vascular remodeling. *Arterioscler Thromb Vasc Biol*. 2010;30:464-470.
22. Chen H, Chen T, Lin H. Prostacyclin-induced peroxisome proliferator-activated receptor-alpha translocation attenuates NF-kappaB and TNF-alpha activation after renal ischemia-reperfusion injury. *Am J Physiol Renal Physiol*. 2009;297:F1109-F1118.
23. Cheng C, Lian W, Chen S, et al. Protective effects of adiponectin against renal ischemia-reperfusion injury via prostacyclin-PPARα-heme oxygenase-1 signaling pathway. *J Cell Physiol*. 2012;227:239-249.
24. Windeløv NA, Ostrowski SR, Perner A, Johansson PI. Transfusion requirements and clinical outcome in intensive care patients receiving continuous renal replacement therapy: comparison of prostacyclin vs. heparin prefilter administration. *Blood Coagul Fibrinolysis*. 2010;21:414-419.
25. Johansson PI, Mortensen CR, Nielsen T, et al. The effect of intraoperative and 6-h postoperative intravenous administration of low-dose prostacyclin on the endothelium, hemostasis, and hemodynamics in patients undergoing a pancreaticoduodenoctemy: a randomized-controlled pilot study. *Eur J Gastroenterol Hepatol*. 2017;29:400-406.
26. Berthelsen RE, Ostrowski SR, Bestle MH, Johansson PI. Co-administration of iloprost and eptifibatide in septic shock (CO-ILEPSS)-a randomised, controlled, double-blind investigator-initiated trial investigating safety and efficacy. *Crit Care*. 2019;23:301.
27. Johansson PI, Søe-Jensen P, Bestle MH, et al. Prostacyclin in mechanically ventilated patients with COVID-19 and severe Endotheliopathy: a multicenter, randomized, clinical trial. *Am J Respir Crit Care Med*. 2022;205:324-329.
28. Bestle MH, Stensballe J, Lange T, et al. Iloprost and organ dysfunction in adults with septic shock and endotheliopathy. *JAMA Netw Open*. 2024;7:e2432444.
29. Schulz KF, Altman DG, Moher D, CONSORT Group. Statement: updated guidelines for reporting parallel group randomised trials. *Ann Intern Med*. 2010;2010(152):726-732.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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