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RESEARCH PROTOCOL

The characteristics of the continuously-recorded mechanical power and its associated clinical outcomes in medical patients with respiratory failure (CORE POWER) study: The protocol of prospective observation study.

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D.J. will receive a share of incomes from Mahidol University if such incomes would occurred from the commercial use of the MAFAI VENT: DRACO Software.

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ABSTRACT:

Background: The amount of energy delivered from the ventilator applied to the lungs within a given timeframe, is defined as mechanical power (MP). Recently, low MP is one of the new concepts in lung-protective ventilation strategies that may associate with survival benefit. However, measuring MP requires additional calculations not being carried-out in usual clinical care and the reports about MP were mostly a cross-sectional data. The real-time changes or dynamic data of MP was scarcely reported. Our objective is to investgate the association between the dynamic changes of MP and clinical outcomes in critically ill patients.

Methods: This will be a prospective, observational study performed in a single center. Adult patients admitted to medical intermediate and intensive care units who requiring invasive mechanical ventilation will be consecutively enrolled. The patients' ventilators will be connected to the specific investigator's computer system for continuously real-time data recording for at least 24 hours. The primary outcome is in-hospital mortality.

Hypothesis: We hypothesize that excessive mechanical power during mechanical ventilation contributes to ventilator-induced lung injury, thus real-time continuously mechanical power monitoring may reduce adverse events associated with mechanical ventilation.

Ethic: The study protocol has been approved by the Institution Review Board of Ramathibodi Hospital, Mahidol University, Thailand (No. MURA2021/680).

Trial registration: TCTR20220202010

Keywords: Mechanical power, Ventilator-induced lung injury, Mechanical ventilation, Respiratory failure, Critically ill

INTRODUCTION

Mechanical ventilation is one of the mostly-used supportive treatments for critically ill patients with acute respiratory failure in the intensive care units (ICU). While this was aimed to decrease the patients' work of breathing, it can conversely cause further lung injuries if inappropriately used [1].

Each breath delivered by the mechanical ventilator inflicts a certain amount of energy on the patient's respiratory system. This energy is mainly used to overcome the resistance of the airways and elastance of the respiratory system. Simultaneously, this energy produced heat or inflammation, probably bring about the injury of the lungs, a phenomenon commonly called "ventilator-induced lung injury" (VILI). The main pathophysiology of VILI resulted from direct injuries to the lung structures by ventilators' forces and mechanotransduction. The cells respond to these physical forces by activation of intracellular biochemical pathways resulting in the release of various inflammatory mediators [2,3].

The amount of energy transferred from the ventilator to the patient is measured in joules (J), while mechanical power (MP) is the total energy expended over a period of time and is usually expressed as joules per minute (J/min). The ventilatory settings which provided by the clinician i.e. tidal volume, inspiratory pressure, respiratory rate, positive end expiratory pressure (PEEP) and flow, had contributed to the mechanical power. All of these parameters has been individually reported to influence VILI. Therefore, the degree of VILI may be related to the mechanical power, which is the product of all these ventilator settings combined [4-6].

Since the year 2000, several studies have suggested lung-protective strategies to minimize VILI such as low tidal volumes to lower the plateau pressure [7], more "open" lung approach [8], or lower driving pressure [9]. Recently, a new concept of safe mechanical ventilation using low MP was presented [5-6]. Previous experimental study in the healthy piglets suggested that the MP exceeding 12 J/min could generate VILI. Furthermore, high MP was associated with increase in lung eleastance and decrease in PaO2/FIO2 ratio [10]. Neto et al.[11] were the first to reported that high MP, especially higher than 17 J/min, is independently associated with higher in-hospital mortality, a lower number of ventilator-free days and longer hospitalization. Moreover, MP was also studied in patients with acute respiratory disease syndrome (ARDS) [12-17], including patients with extracorporeal membrane oxygenation (ECMO) [14,16]. Also, M. Urner and colleagues reported a patient who had long exposure to higher MP intensity was associated with higher mortality in ICU [18]. Thus, limiting exposure to high MP might be recognized as part of the individualized lung-protective ventilation strategy to minimize VILI. Up to now, the safety mechanical threshold remains unclear.

Each aforementioned study reported differ relationship between the MP alone and the intensive care mortality, while MP normalized to the patient's predicted body weight [12], normalized to the amount of well-inflated tissue, and normalized to respiratory system compliance [13,14], independently influenced the ICU outcomes. Most studies were retrospective in nature [11-15], and all had used a simplified equation proposed by Gattinoni et al. [5] to calculate MP. This equation was limited to the patients using volume-controlled ventilation mode only and, to our knowledge, the continuously-recorded mechanical power of patients under other ventilation modes, particularly the pressure-controlled, has never been systematically investigated. Thus, the conclusion regarding a relationship between MP and mortality is still vague and requires more solid evidence.

KEY MESSAGES:

- Mechanical power (MP) has gained more interest during the recent years and might be an important factor determining lung injuries during mechanical ventilation.
- In this study, we aim to collect the real-time changes or dynamic data of MP and find its association with clinical outcomes.

OBJECTIVES

1. To study the impact of the continuously-recorded MP and its variation on the clinical outcomes of medical patients with respiratory failure
2. To find the components of the mechanical power that affects the patients' clinical outcomes.

MATERIALS AND METHODS

Study Design

This single-center, prospective, observational study has been planned to take place between October 2021 and February 2022.

Study Setting

The study will be conducted at the medical intermediate ward and medical ICU of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Study population

We will consecutively enroll new adult patients older than 15 years who are admitted to medical intermediate and ICU due to acute respiratory failure of various causes requiring invasive mechanical ventilation.

Inclusion criteria

1. Using ventilators those are capable of exporting real-time signal to the specifically designed data collecting system (Technically limited to Puritan-Bennett ventilator model PB840 or PB980)
2. Receiving invasive ventilation for at least 24 consecutive hours
3. Able to perform data collection within 24 hours after connected to the current mechanical ventilator
4. Receiving permission from the attending physician.

Exclusion criteria

1. The patient who is extubated or die or discharge from the ICU during the first 24 hours

2. The patient who was previously enrolled in this study
3. The patient was intubated and admitted to the ICU more than once during the same hospitalization
4. The patient was intubated and admitted to the ICU more than once during the same hospitalization.
5. The patients who denied participation in the study.

Consent

Once the patients meet certain eligible criteria. The investigator performs inform-consent within 24 hours after ICU admission. Patients or the patients' next of kin received the information they require to make a decision to volunteer and ask questions about the study protocol. The patient's data collection was established after the informed consent is obtained.

Study procedures

After the informed consent is obtained, we will record the baseline characteristics including age, gender, body weight, height, body mass index, smoking status, vital signs, inotropic and vasopressor use, acute physiology and chronic health evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) Score at ICU admission (where available), Glasgow Coma score, PaO2/FiO2 ratio, hospital arrival time, intubation time, ICU admission time, cause of endotracheal intubation and the patients' underlying diseases especially cardiopulmonary disease. Baseline mechanical ventilator settings that is provided by the primary physician (mode, airway pressure or tidal volume, flow or inspiratory time or expiratory trigger sensitivity, flow wave pattern, respiratory rate, PEEP, FiO2) will be noted. The patient's ventilator data port was linked and connected through the WiFi system to the central investigator's computer system, using a specifically designed program (MAFAI VENT: DRACO Software version 2.13, Mahidol University, Bangkok, Thailand) which operated on Microsoft Excel 2016 (Microsoft, Washington, USA). Without changing any ventilator settings and treatments provided by the primary physician, the flow and pressure data (with a sampling rate of 50 Hz) will be continuously interpreted into numerical values, including the tidal volume, PEEP, plateau pressure, driving pressure, respiratory rate, minute ventilation, and compliance (where available). The energy applied per breath has been measured using the dynamic pressure-volume curve recorded. The program automatically and continuously integrates the area between the inspiratory volume-pressure curve and the volume axis in each breath to yield the MP, which will be multiplied by the average respiratory rate to get the MP per minute (the geometric method), considered the gold standard. The data from all breaths in a minute is averaged in form of median and recorded as the representative value for that particular minute (median MP every 1 minute) and stored into a table format which can be later exported for analysis. . We will continuously record all the data during the first 24 hours of ventilator connection. We concerned about the variation of these time series data, thus we used the median of the median of MP every 1 minute entire 24 hours as a representative value for analysis.

After that, data will be extracted and then analyzed offline. The clinical outcomes of the patients would be collected by subsequent electronic medical-records review. (Figure1)

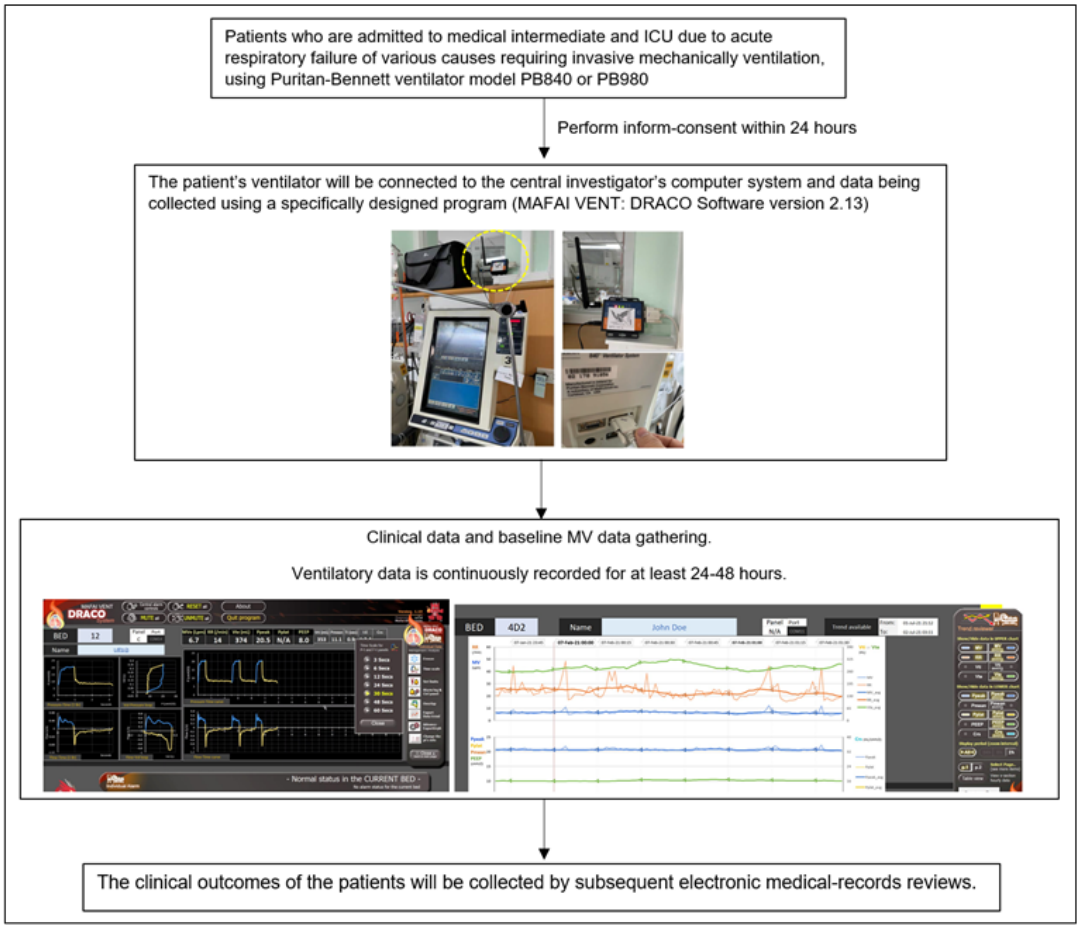

Figure 1. The flowchart of data collection

Adverse events
Unexpected adverse events have scarcely occurred throughout data collection because our protocol did not change any ventilator settings and treatments provided by the primary physician. However, If an adverse event happens during data collection, the investigator will notify the attending physician immediately.

Outcome measurement
The primary outcome was in-hospital mortality. Secondary outcomes included 28-day mortality, ICU length of stay, hospital length of stay, duration of intubation, ventilator free-days in 28 days, and respiratory complications associated with mechanical ventilation.

Exploratory outcomes -

Timeline
As shown in figure 1.

DATA ANALYSIS PLAN

Sample size calculation
For the sample size calculation, at the time of study-design contemplation, there was inadequate published data using the same measurements method or performed within similar population to conclude the sample size. We thus aim to consecutively enrolled patients into this study for at least 5 months and perform preliminary data analysis. The actual study period might be extended according to the preliminary result.

OUTCOME ANALYSIS PLAN

Statistical analysis
Continuous variables will be presented as mean ± standard deviation (SD) or median and interquartile range (IQR) where appropriate. Categorical variables will be presented as numbers and percentages.

For the mechanical power, the dynamic changes of the parameters (e.g. percentage of variation from the baseline, or the value-time above the specific threshold [11] will also be calculated.

Statistical analysis will be conducted with SPSS version 22.0 software (IBM SPSS Statistics, IBM corporation, New York, USA) and significance level would be set at p-value <0.05. Comparisons of ventilatory variables between the two groups with different clinical outcomes (e.g. non-survivors vs. survivors) will be made with Chi-Square or Fisher's exact test in case of categorical parameters and unpaired T-test or Mann-Whitney U test in case of continuous parameters. For clinical outcomes with continuous nature (e.g. ventilator free days, hospital or ICU length of stay), Pearson's or Spearman's correlation will be applied.

DATA MANAGEMENT AND DATA MONITORING

Input data and monitoring method
Baseline patient characteristics variables (Table 1)
Lung mechanics variables (Table 2)
Patient's outcomes (Table 3)

Table 1. Baseline patient characteristics variables

Baseline patient characteristics	Collection method
Gender	Chart review
Age (years)	Chart review
Weight (kg)	Chart review
Height (cm)	Chart review
BMI	Chart review, Manual calculation
Smoking status	Chart review
Vital signs; mean Body temp (c) Pulse rate (bpm) Respiratory rate (/min) Systolic BP (mmHg) Mean BP (mmHg) Oxygen saturation at baseline	Chart review
Vasopressor used	Chart review
Glasgow Coma score	Chart review
APACHE II score, SOFA score	Chart review
Parameter from ABG Calculated PaO_2/FiO_2	Chart review
Cause of ETT intubation Pulmonary cause -Pneumonia -COPD with acute exacerbation -ARDS -Tracheobronchitis -Upper airway obstruction, Secretion obstruction -Hemoptysis -Acute asthmatic attack -Infected bronchiectasis -Pleural effusion -BO/ small airway disease -Pneumothorax Hemodynamic cause -Septic shock -Post cardiac arrest Neurological cause Post-procedure/operation/airway -protection Cardiogenic pulmonary edema and -volume overload Other	Chart review
Underlying disease (can be >1 diseases per patient) Chronic cardiac disease -Hypertension -Ischemic heart disease -Atrial fibrillation -Left ventricular dysfunction or History of cardiogenic pulmonary edema Chronic lung disease -Chronic obstructive pulmonary disease -Primary lung cancer -Chronic restrictive extrapulmonary disease -Asthma -Fibrotic lung disease	Chart review

Table 1. (Continued) Baseline patient characteristics variables

Baseline patient characteristics	Collection method
-Obstructive sleep apnea -Bronchiectasis -Tracheobronchomalacia Neurological disease Chronic kidney disease	

Table 2. Data of lung mechanics

Lung mechanics in first 24 hours	Collection method
Minute ventilation (L/min)	Extracted data from DRACO software
Respiratory rate (bpm)	
Exhaled tidal volume (ml/PBW)	
Peak inspiratory pressure (cmH_2O)	
PEEP (cmH_2O)	
Inspiratory time (second)	
Baseline mechanical power (J/min)	
Mechanical power ≥ median MP; n(%)	
Mechanical power ≥19 J/min; n(%)	
Duration of mechanical power ≥ median MP (%); median	
Duration of mechanical power ≥19 J/min (%); median	
Duration of data recording within first 24 hours (hours)	

Table 3. Patient's outcomes

Outcomes	Collection method
Hospital mortality	Chart review
28-day mortality	Discharge summary review, telephone
Hospital length of stay	Chart review
Duration of intubation	Chart review
Ventilator free days in 28 days	Chart review
Respiratory complications associated with mechanical ventilation.	Chart review

DISCUSSION

We are conducting the trial to investigate the association between the dynamic values of MP and clinical outcomes in critically ill patients using DRACO software. Originally, the MP was mathematically computed with the equation proposed by Gattinoni and enrolling volume-controlled mechanically ventilated patients [5]. Previously published studies on the concept of MP have several limitations. First, most studies have focused on passive ventilation, particularly volume-controlled ventilation. Second, Most studies were retrospective analyses. Finally, the ventilatory variables did not record in continuous data. Our study showed the new practicability of the geometric method, as a gold standard, using the DRACO program which could be performed in routine clinical practice. The main advantages of this method are simplicity, no need for any clinical procedure on the ventilator (such as an inspiratory pause),

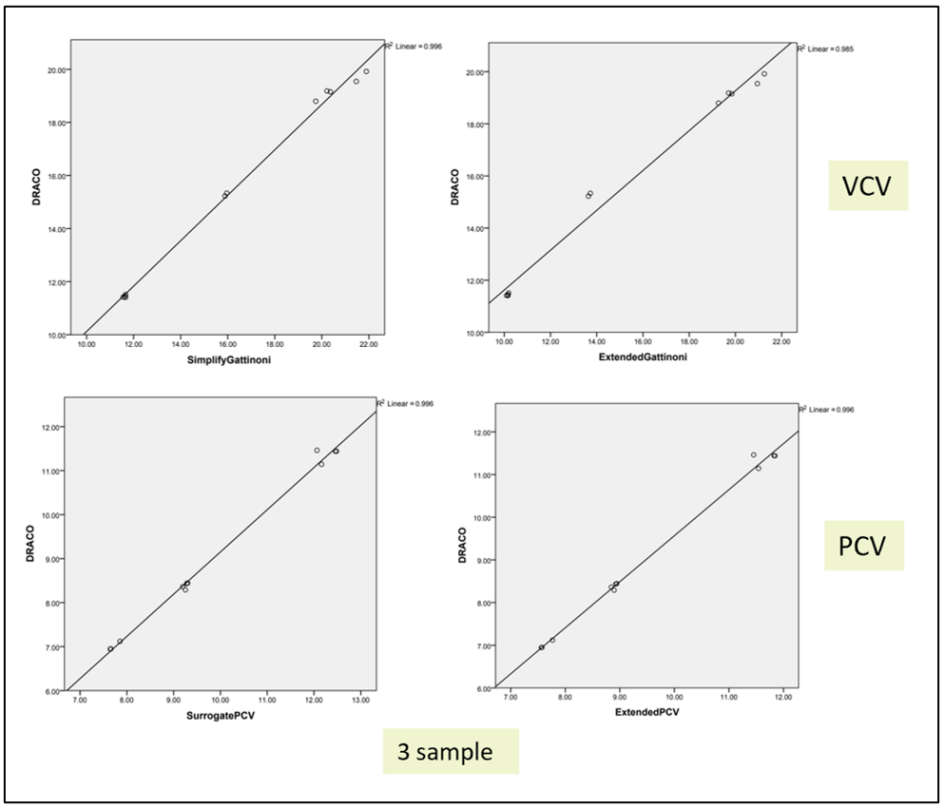

Figure 2. The relationship between mechanical power measurement using DRACO program and the surrogate equation proposed

availability in all modes of the ventilator, and can be currently useful in non-sedated and paralyzed patients with spontaneous breathing. Before using mentioned MP measurement, we tested the validity of the geometric method using the DRACO software and compared it with the surrogate formulas of MP were proposed [19]. The regression between the MP calculated by the geometric method (DRACO) and the comprehensive algebraic formulas was well correlated with R2 of 0.9 (Figure 2).

Previous existing studies demonstrated that high MP was associated with increased hospital death, but the cutoff value for high MP was different in each study. We set the two thresholds of high MP for an outcome analysis, which one was from our median MP and 19 J/min according to the study of Neto et al. [11].

Strengths

- First prospective study, MP record was calculated using analysis of PV curves while in spontaneous breathing
- Perform a new feasible test to detect MP
- Lung mechanics were real-time continuously recorded during the intensive care stay.
- Our study included all kinds of respiratory failure, which makes the results generalizable.

Limitations

- Small sample size over a short time frame
- Limited number of critically ill patients due to COVID-19 pandemic era
- Different determination of the onset of data recording
- We did not collect data beyond the first 24 hour study period.

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AUTHORS' CONTRIBUTIONS

D.J. and P.T. were involved in the conception, design of the study protocol and will supervise the study. D.J. designed the specifically data collecting system [DRACO system] and its software component [MAFAI VENT: DRACO Software]. A.K. will collect all patient's data, complete the study database and write original drafting of the manuscript. A.K and D.J. will perform the statistical analysis of data and interpret the results. D.J. and P.T. will contribute with important review and editing of the final manuscript. All authors have read and agreed to the published version of this protocol manuscript.

SUPPLEMENTARY MATERIALS

none

ABBREVIATIONS

APACHE, Acute physiology and chronic health evaluation; ARDS, Acute respiratory distress syndrome; ARF, Acute respiratory failure; ATC, Automatic tube compensation; BMI, Body mass index; CPAP, Continuous positive airway pressure; COPD, Chronic obstructive pulmonary disease; DE, Diaphragm excursion; DTF, Diaphragm thickness fraction; HFNC, High-flow nasal cannula; ICU, Intensive care unit; NIV, Noninvasive ventilation; Paw, Airway pressure; PCV, Peak contraction velocity; PRV, Peak relaxation velocity; PSV, Pressure support ventilation; RR, Respiratory rate; RSBI, Rapid shallow breathing index; SBT, Spontaneous breathing trial; Tdi, Diaphragm thickness; TDI, Tissue doppler imaging; TDI-MRR, Tissue doppler imaging - derived maximal relaxation rate; Ti, Inspiratory time; VT, Tidal volume; VTI, Velocity time integral.

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