SUPPLEMENTAL DIGITAL CONTENT 1

Statistical analysis plan and IRB approval

Mechanical power during general anaesthesia and postoperative respiratory failure: A multicentre retrospective cohort study

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Original date 12/12/2020

Updates during the review stage:

Update 10/03/2021:

- *As requested by reviewers, the model throughout all analyses will be changed to a mixed effects logistic regression model including the study site as random effects. It will further include the year of surgery, instead of in a sensitivity analysis. Sugammadex administration will be added to the confounder model and neostigmine dose will be adjusted for bodyweight (mcg/kg).*
- *As requested by reviewers, we will conduct multiple exploratory analyses to expand knowledge on exposure-outcome association: (1) we will investigate the effect of intraoperative fluid administration on temporal increases of mechanical power; (2) we will investigate the characteristics of exposure and outcome per year of surgery; (3) we will investigate the association between mechanical power and early (postoperative days 0-3) versus late (postoperative days 4-7) re-intubation after surgery; (4) We will investigate the commonly used composite outcome of postoperative pulmonary complications, defined as atelectasis, pneumonia, respiratory failure, and exacerbation of underlying chronic lung disease; (5) effect modification analysis by the depth of neuromuscular blocking; (6) effect modification analysis by the mode of ventilation, categorized into pressure control ventilation vs other modes of ventilation; and finally (7) we will conduct interaction term analysis by the most prominently imbalanced confounding variables.*
- *As requested by reviewers, we will add multiple sensitivity analyses that include: (1) exclusion of thoracic surgery cases; (2) exclusion of patients who received blood transfusion; (3) we will investigate provider effects in additional analyses. Provider variability in the use of high mechanical power will be assessed and the individual anesthesia provider will be added as a random effect to the model in a sensitivity analysis, nesting random effects for anesthesia providers in the random effects model for the study center; (4) we will conduct bootstrapping for our primary model; and finally (5) we will test the robustness of our primary results using inverse probability of treatment weighting.*

Update 04/10/2021:

In response to a recent publication (10.1164/rccm.202009-3467OC), exploratory analyses will be conducted investigating the association of the individual components of mechanical power (static, dynamic resistive and dynamic elastic) with the primary outcome in a separate statistical model.

Update 03/01/2021:

In additional exploratory analyses, we will investigate how temporal trends in mechanical power during surgery differ between patients with and without postoperative re-intubation. We will further calculate and compare the adjusted risk of re-intubation for different thresholds of increases in mechanical power.

Sensitivity analyses added:

- Calculation of mechanical power on a minute-by-minute basis in patients with available data
- Exclusion of patients without available plateau pressure
- Adjustment for PaCO2, PaO2/FiO2 and the gradient between PaCO2 and etCO2, where blood gas analyses available

Background

Approximately 300 million noncardiac surgeries are performed worldwide every year and this number continues to increase. About 3-7% of patients undergoing noncardiac surgery under general anesthesia develop postoperative respiratory complications, which are associated with increased mortality and hospital costs. Previous studies demonstrated that static parameters of intraoperative mechanical ventilation such as tidal volume and inspiratory pressure are closely associated with a patient's risk of postoperative respiratory complications by promoting ventilator-induced lung injury. Newer studies further suggested that dynamic parameters such as the intraoperative respiratory rate increase postoperative respiratory complications. There is evidence from mechanical ventilation in the intensive care unit that the interplay between these parameters plays an important role in promoting ventilator-induced lung injury. Recently, a measure that integrates these static and dynamic parameters - Mechanical Power - has been proposed. Mechanical Power estimates the energy delivered to the Respiratory System per minute and has been associated with patient outcome in the intensive care unit. However, so far there has been no

study that investigated the association between mechanical power and clinical outcome in patients undergoing mechanical ventilation in the operating room. With a simplified equation, mechanical power can be calculated from anesthesia records using tidal volume, inspiratory pressure and respiratory rate. Therefore, we hypothesize that the intraoperative mechanical power is associated with postoperative pulmonary complications. We further hypothesize that intraoperative mechanical power predicts postoperative pulmonary complications better than tidal volume, inspiratory pressure, or respiratory rate alone. To investigate these hypotheses, we plan to conduct retrospective analyses from hospital registry data from two different hospitals (BIDMC & MGH).

Primary objective

This study is designed to investigate the primary hypothesis whether higher mechanical power is associated with increased risk of postoperative pulmonary complications, measured by the primary outcome postoperative re-intubation within seven days and the secondary outcome postoperative de-saturation.

Inclusion criteria

The subject population will be an adult surgical patient cohort undergoing general anesthesia.

Exclusion criteria

- Age <18
- ASA > IV
- Cardiac surgery
- Emergency surgery

Statistical methodology

Data management

Massachusetts General Hospital

Patient data are collected via the Anesthesia Information Management System (AIMS) and the Research Patient Data Registry (RPDR), a centralized clinical data warehouse that compiles health records and billing data from 53 various Partners hospital systems specifically for research purposes. Mortality data will be derived from the Enterprise Performance Systems Inc. (EPSi).

Beth Israel Deaconess Medical Center

Patient data are collected from AIMS and the Perioperative Information Management System (PIMS). AIMS includes information pertaining to perioperative anesthetic management while PIMS includes surgical data. Current Procedural Terminology (CPT) codes for procedural severity will be gathered from the Center for Clinical Computing (CCC) anesthesia billing database. Comorbidities and admission/discharge information will be obtained from Casemix and from the Admission Discharge Transfer (ADT) database. Mortality data will be obtained through the Miscellaneous (MISC) database.

Exposures

The primary exposure variable will be the median intraoperative mechanical power, calculated by the formula $Mechanical\ Power\ (J/min) = 0.098 * Respiratory\ Rate * Tidal\ Volume * [P_{peak} - ½(P_{plat} - PEEP)]$.

Outcomes

The primary outcome variable will be postoperative re-intubation within seven days. The secondary outcome will be post-extubation desaturation <90% hemoglobin saturation within 10 minutes.

Statistical Methods

95% confidence intervals will be calculated for odds ratios, relative risks and risk differences. A two-sided alpha will be set to 0.05. Data management and statistical analyses will be performed using Stata software (StataCorp, College Station, Texas, USA), version 13.0 or newer, and RStudio (Rstudio Inc., Boston, Massachusetts, USA).

Our pre-specified primary analytic strategy will be a logistic regression analysis to investigate the association between mechanical power and postoperative respiratory complications and to address potential confounding. Analyses will be adjusted for potential confounders including patient, anesthesiologist, and procedural variables using a set of a priori selected variables based on a literature search, clinical, and biological plausibility. Therefore, the confounder model will consist of the study site, as well as patient-specific confounders: age, sex, body mass index, ASA physical status, Charlson Comorbidity Index, history of smoking, and diagnoses of heart failure or chronic obstructive pulmonary disease; Procedure-related confounders: surgical service, duration of surgery, high-risk surgery, work relative value units, Score for Prediction of Postoperative Respiratory Complications ≥7), time with mean arterial pressure <55 mmHg, vasopressor dose, fluid volume, packed red blood cell units, doses of short and long-acting opioids, ED95 of NMBA, neostigmine dose, age-adjusted minimum alveolar concentration of inhalational anesthetics, fraction of inspired oxygen (FiO_2), and airway device.

In secondary analyses, we will construct additional statistical models to investigate whether Mechanical Power is statistically associated with the primary outcome after additionally adjusting for components of its calculation, including tidal volume, respiratory rate and driving pressure.

Sensitivity analyses

We will conduct multiple sensitivity analyses to assess robustness of the primary study findings: (1) To address a potential non-linear relationship, we will re-define the exposure by categorizing mechanical power into quintiles; (2) we will adjust mechanical power for ideal body weight and body mass index and repeat the primary analysis; (3) in a subgroup of patients with available minute-by-minute ventilator data, we will re-define the exposure variable by calculating mechanical power on a minute-by-minute basis; (4) we will repeat the primary analysis in the

subgroup of patients with available plateau pressure measurements; (5) we will exclude patients receiving laryngeal mask airways, or (6) undergoing laparoscopic surgeries; (7) we will conduct subgroup analyses in inpatients with duration of surgery of ≥3 hours to test robustness of findings in this high risk group, as well as thoracic surgery cases; (8) In a subgroup with available arterial blood gas analyses, we will adjust the primary analysis for arterial carbon dioxide partial pressure ($PaCO_2$), arterial oxygen partial pressure to inspiratory oxygen fraction (PaO_2/FiO_2) ratio and $PaCO_2$ to end-tidal carbon dioxide ($etCO_2$) gradient as a marker of the degree of physiological dead space; (9) To address missing confounder data, we will perform multiple imputation for any variable with missing data and repeat the primary analysis in the imputed cohort.

IRB approval

Beth Israel Deaconess Medical Center | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Committee on Clinical Investigations
330 Brookline Ave.
Boston, MA 02215
(617) 975-8511

Association for the Accreditation of Human Research Protection Programs, Inc. — Full Accreditation

Determination of Exemption

IRB Protocol #:	2020P001072
Principal Investigator:	Maximilian Schaefer
Protocol Title:	The association between mechanical power and the risk for postoperative respiratory complications in patients undergoing general anesthesia
Funding:	Internal -
Review Type:	Exempt - Categories: 4
IRB Determination Date:	12/09/2020
Notification Date:	12/16/2020

The Beth Israel Deaconess Medical Center Committee on Clinical Investigations has determined that the referenced application meets the criteria for exempt status under exempt category/categories: 4.

HIPAA Waiver of Authorization is approved.

Please Note: A Data Usage Agreement (DUA) is required, please contact your Department Research Administrator.

When the CCI determines that a study is exempt continuing review and approval is not required. In some circumstances, modifications to exempt research disqualify the research from the exempt status. Modifications that could increase the risk level, alter the study design or population, or involve a change in PI must be submitted to the CCI for review and approval prior to implementation.

PLEASE NOTE:

You are reminded that you are required to follow the requirements described in the CCI Policy and Procedure Manual.

If there are any questions you may contact the Committee on Clinical Investigations (CCI) at 617-975-8511.

cc: Elias Baedorf Kassis, Peter Santer

Mass General Brigham IRB
Mass General Brigham
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Notification of IRB Review

Protocol #: 2020P003633

Date:	November 20, 2020
To:	Houle, Timothy MGH Mass General Brigham > MGH > Anesthesia
From:	Mass General Brigham IRB 399 Revolution Drive, Suite 710 Somerville, MA 02145
Title of Protocol:	The association between mechanical power and the risk for postoperative respiratory complications in patients undergoing general anesthesia
Version/Number:	
Version Date:	
IRB Review Type:	Expedited
IRB Review Action:	Exempt
IRB Approval Date:	11/20/2020
Approval/Activation Date:	11/20/2020
Next Review:	**Exempt Check In**
IRB Expiration Date:	**11/20/2023**

The IRB has determined that this project meets the criteria for exemption 45 CFR 46.101(b)(#)

Note: IRB approval of research does NOT constitute final approval to conduct the research. Human subjects research must be conducted in accordance with MGB's Expansion Plan of Clinical Research.

EXEMPTION (4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least ONE of the following criteria is met:

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined

As Principal Investigator, you are responsible for the following:

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1. Ensuring that this project is conducted in compliance with this determination.
2. Ensuring that all study staff have completed the required human research education requirements through the Collaborative Institutional Training Initiative (CITI).
3. Submission of significant proposed changes to this project to ensure that the project continues to meet the criteria for exemption.
4. Submission of Exempt Check-In every 3 years as required by institutional policy.

Questions related to this project may be directed to **Fred Syllien | Tel: 857-282-1905 | Email: FSYLLIEN@PARTNERS.ORG**

cc:

Timothy Houle, Principal Investigator, Anesthesia