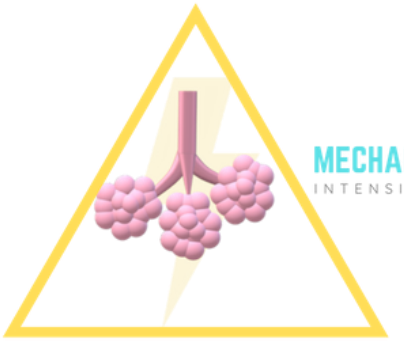

MECHANICAL POWER DAY
INTENSIVE CARE CLINICS

ASSESSMENT OF THE MECHANICAL POWER TRANSMITTED TO THE PATIENTS WITH MECHANICAL VENTILATION IN INTENSIVE CARE UNITS "MECHANICAL POWER DAY"

Research protocol

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Content index

Introduction and justification:

Over the last few years we have witnessed an important technological developement in the field of mechanical ventilation. Along with the technological advances, the better understanding of the respiratory physiopathology has shown that mechanical ventilation "per se" can lead to deleterious effects.

In this context, the search for those variables which are responsible for the developing of ventilator-induced lung injury (VILI) has become an important goal in this field. In fact, we are witnessing the nearly exponential increase in the publication of studies that have tried to associate the different parameters that intervene in mechanical ventilation with the injury to the lung structure.

Recently the new concept of "mechanical power" has been proposed. It refers to the amount of energy per minute that is transferred to the lung by the ventilator. The generation of this form of energy would include both parameters that were previously proposed to be possible causes for lung damage and new parameters that had not been taken into account until now, such as the flow rate or the respiratory rate, without forgetting the individual characteristics of each ventilated subject.

12J/min has been stablished experimentally as the energy threshold from where changes in the lung that can lead to VILI begin to appear. Nevertheless, the true issue would be to get to know the best way to normalize the mechanical power value. However, it seems reasonable to think that the values of energy originating VILI in experimental animal models and in humans are different.

Nowadays, in spite of the wide range of monitoring systems that we have, we still don´t know the real mechanical power that we are transmitting to our patients. The different research teams that have deepened into the subject have seen themselves forced to infer their results from retrospective data and from very selected samples of patients immersed in different studies. As one of the first steps in the way of a better understanding of the impact of "mechanical power", we believe it is justified to develope a descriptive and observational study to get to know the real mechanical power value we ventilate our patients in the ICU with.

Objective and hypothesis:

Clinical guides and recommendations aimed at improving ventilation basing on the characteristics of the different pathologies in order to minimize VILI do exist, but the fact remains that the threshold of mechanical power in mechanical ventilation is still unkown.

The main hypothesis of the present study is that the mechanical power received by the patients who need mechanical ventilation in the intensive care unis is greater tan the threshold that has been established by experimental models.

Moreover, we think that mechanical power varies considerably depending on the current and previous pathology of the patient and the days on mechanical ventilation.

Resting on the previous hypothesis, the main objective of the current study is:

- Know the value of the mechanical power in the patient connected to mechanical ventilation, in a volume control model.

This value will be calculated from electronically provided data using the simplified formula by Gattinonni et. Al.

Secondary objectives are:

- Analyze the epidemiology of different modalities in ventilatory, not just VC, on the basis of the collected variables.
- To assess if the transmitted mechanical power varies depending on the pathology, on the days on mechanical ventilation or on the reason that leads to the need for mechanical ventilation.
- In case of a ventilatory mode which allows spontaneus breathing, we can see the variability of the plateau pressure and if we can infer its value in the calculation of mechanical power.
- To know the driving pressure and the ventilatory ratio of ventiled patients.
- To establish differences among the main analysed parameters depending on the type of critical carea area studied.

Design and methodology:

Observational, prospective and analytical study.

The variables of the study will be collected on a fixed date as agreed with the participating ICU. These variables will be registered during the period of time between 8 am to 15 pm

on the 21st of November 2019, in order to adjust to the normal working routine at an intensive care unit.

The study will consist of a second phase, scheduled for December 19, that includes data on the clinical evolution of patients included in the registry on November 21.

Sample selection:

All patients that are hospitalised in a critical care unit and on mechanical ventilation on the 21st of November 2019.

Inclusion criteria:

All the patients hospitalised in a crital care unit who are on invasive mechanical ventilation, whatever the cause.

Exclusion criteria:

Admitted patients who are not on mechanical ventilation at the specific point of time.

Those patients who have been on mechanical ventilation for less that 6 hours are excluded.

Patients who are on mechanical ventilation through a tracheostomy are excluded.

Patients who are ventilated on APRV or BiLEVEL mode are excluded.

Patients on noninvasive ventilation are excluded.

Patients undergoing nasotracheal intubation are excluded

Patients on selective lung ventilation are also excluded.

Patients with extracorporeal circulatory and respiratory support (ECMO-VV and ECMO-VA) are excluded.

Required intervention:

Given the observational nature of this study, we consider that no intervention is required. Participation in concomitant studies: given the observational condition of this study, patiens that are included in other observational and/or experimental researches, can be included in the current study.

Data collection:

A cross-section will be made on the 21st of November 2019 and all patients who are hospitalised in an intensive care unit and on mechanical ventilation and who meet the inclusión criteria, will be included in the study.

A second cross section will be carried out on December 19, in which data derived from the clinical evolution of patients included in the registry will be collected on November 21.

The study variables will be collected on a paper case report form (CRF). Later on, data will be trasncribed from paper CRF to electronic CRF. (Didacticaweb, Avd. Pablo Iglesias 85 i 3B, 28521 Rivas Vaciamadrid, Madrid, España, 09387163N).

Data collection will be supervised by the designated researcher from each center.

Study variables:

Demographic, clinical and analytical data are prospectively reviewed from the medical history, either paper-based or electronically recorded.

The following variables will be recorded: healthcare center where the patient is registered, identification number given by the own center (this number may not be the same as the patient medical record number), some variables related to demographic and clinical data as well as personal pathological antecedents, some variables related to mechanical ventilation: ventilator model, ventilatory mode, tidal volumen (cc), PEEP (cmH20), mandatory respiratory rate (rpm), spontaneous respiratory rate (rpm), inspiratory time (s), peak pressure (cmH20), plateau pressure (cmH20), Vd/Vt (%), ETCO2 (mmHg), compliance (cc/cmH2O), FiO2 (%) and some analytical variables: pH, pO2 (if arterial blood gas is available), SatO2 (if arterial blood gas is not available), pCO2, HCO3, base excess, lactate, SatVO2.

Variable definitions:

- **Demographic variables**

*Hospital: healthcare centre that registers the patient.

*Identification number: number given to each registered patient by the own healthcare centre. It is different from the patient medical record number.

- **Personal and pathological antecedents**

* Date of birth: temporary variable.

* Gestational age: for those pediatric patients. Quantitative variable.

*Gender: male or female. Qualitative variable.

*Height: length from feet to head (estimation from knee-heel length is also accepted). Measure in cm. Quantitative variable.

*Weight: body mass in kilograms. Quantitative variable.

*Smoker: active smoking habit. Dichotomous variable: yes or no.

*COPD: previous diagnosis of chronic obstructive pulmonary disease whatever the cause or severity, with or without pulmonary function test. Dichotomous variable: yes or no.

*GOLD C or D COPD: previous diagnosis of chronic obstructive pulmonary disease GOLD C or D whatever the cause. Dichotomous variable: yes or no.

*Asthma: previous diagnosis of asthma whatever the cause or severity. Dichotomous variable: yes or no.

*Active pulmonary neoplasm: previous diagnosis of any malignant pulmonary tumor, whatever its extention. Dichotomous variable: yes or no.

*Thoracic radiotherapy: previous radiotherapy treatment, whetever ist indication. Dichotomous variable: yes or no.

*Previous lobectomy: previous surgical removal of a lung lobe. Dichotomous variable: yes or no.

*Previous pneumonectomy: previous surgical removal of a lung. Dichotomous variable: yes or no.

*Lung maturation: in pediatric patient, use of drugs to accelerate lung development. Considered as a dichotomous variable as if or not.

*Surfactant administration: in prior antecedent, pediatric patient having administered surfactant. Considered as a dichotomous variable as if or not.

*Bronchopulmonary dysplasia: in pediatric patient, existence of bronchopulmonary dysplasia. Considered as a dichotomous variable as if or not.

*Congenital syndrome: in previous diagnostic, Pediatric congenital syndrome patient. Considered as a dichotomous variable as if or not. If so specify what.

*Congenital heart disease: in previous diagnostic, Pediatric congenital heart disease patient. Considered as a dichotomous variable as if or not. If so specify what.

*Malformation of the airway /Estenosis: in malformation/airway stenosis prior diagnostic pediatric or adult patient. Considered as a dichotomous variable as if or not.

*Others: any other not previously referred lung disease. Qualitative variable.

- **ICU admission related variables**

*Reason for admission: main cause of admission in the intensive care unit. Dichotomous variable: respiratory or not respiratory.

*Date of orotracheal intubation: temporal variable.

*Cause for intubation: understood as qualitative variable: respiratory, hemodynamic, neurological, weaning failure or others.

*Cause for mechanical ventilation (if different from the cause of intubation): understood as qualitative variable: respiratory, hemodynamic, neurological or other.

*Acute Respiratory Distress Syndrome (ARDS): according to Berlin criteria (see annex 1). Qualitative variable.

*Previous noninvasive ventilation (NIV): use of any noninvasive ventilation device (BiPAP, CPAP, high-flow nasal oxygen therapy) before intubation. Dichotomous variable: yes or no.

*Days of previous NIV: number of days on noninvasive ventilation before intubation. Quantitative variable.

*Ventilator-associated complications:

Ventilator associated pneumonia (VAP): developing of pneumonia in a patient in mechanical ventilation after intubation and until the date proposed for the study. (diagnosed according to the criteria of the regulatory agency of each participating country). Dichotomous variable: yes or no.

Pneumothorax: appearance of a pneumothorax of any cause in a patient in mechanical ventilation after intubation and until the date proposed for the study. Dichotomous variable: yes or no.

Others: specify any other complication different form the exposed above.

*Continuous infusion of sedatives: dichotomous variable: yes or no.

*Continuous infusion of analgesics: dichotomous variable: yes or no.

*Continuous infusion of neuromuscular blocking agents: dichotomous variable: yes or no.

*Bolus injection of neuromuscular blocking agents: dichotomous variable: yes or no.

*RASS Scale: numerical quantitative variable (from +4 to -5).

- **Mechanical ventilation related variables**

*Essential variables for the calculation of mechanical power.

*Ventilator model: ventilator brand and model. Qualitative variable.

*Ventilatory mode: description of the ventilatory mode used at the time of registration. Qualitative variable.

*Nº of orotracheal tube: number of orotracheal tube. Qualitative variable

*FiO2 (%): fraction of inspired oxygen. Quantitative variable.

*SatpO2: Oxygen saturation measured by pulse oximetry. Quantitative variable.

*Tidal volumen: tidal volume measured in cc. Quantitative variable.

*Expired tidal volumen: Quantitative variable.

*PEEP: positive end expiratory pressure, without expiratory pause. Measured in cmH_2O. Quantitative variable.

*Mandatory respiratory rate: respiratory rate produced by the ventilator without ventilatory effort from the patient. Measured in rpm in controlled ventilation. Quantitative variable.

*Spontaneus respiratory rate: respiratory rate produced by the patient's own inspiratory effort. Measured in rpm. Quantitative variable.

*Inspiratory time: duration of inspiratory time in seconds. Settled time in controlled modes and time calculated by the ventilator in spontaneous modes. Quantitative variable.

*PIP: Peak inspiratory pressure: measured in cmH_2O. Quantitative variable.

*Plateau pressure: it reflects the alveolar peak pressure and allows the calculation of the static distensibility. See annex III. In cmH_2O. Quantitative variable.

*Driving pressure: (ΔP, driving pressure or airway distending presure): it's the difference between the alveolar pressure at the end of inspiration (plateau pressure) and the positive end expiratory pressure (PEEP). Quantitative variable.

*PSV: pressure support ventilation. Measured in cmH_2O. Quantitative variable.

*VD/VT: ratio of dead space over tidal volume. Provided by the respirator. Percentage. Quantitative variable.

*$ETCO_2$: non-invasive measurement of exhaled CO_2. Quantitative variable.

*Dynamic compliance: distensibility of lung parenchyma. Quantitative variable.

*Airway resistance: resistance of the respiratory tract to airflow. Provided by the respirator. Quantitative variable.

- **Analytical data related variables**

Analytical data will be taken from the routine blood test performed during the morning shift and from the one which is closer in time to the registration of the ventilatory parameters.

Data from arterial blood gas are preferable. If ABG is not available, data from central venous blood gas will be registered.

*pH: blood pH obtained from ABG or VBD. Quantitative variable.

*PO2 (if ABG): partial pressure of oxygen in arterial blood if ABG is available. Quantitative variable.

*SatO2: arterial oxygen saturation measured by pulse oximetry, if ABG is not available. Quantitative variable.

*PCO2: partial pressure of carbon dioxide in arterial blood if ABG is available. Quantitative variable.

*PvCO2: partial pressure of carbon dioxide in venous blood if VBG is available. Quantitative variable.

*HCO3: blood bicarbonate value, from ABG or VBG (in the morning and closer in time to the collection of ventilatory parameters). Quantitative variable.

*BE: base excess value, from ABG or VBG (in the morning and closer in time to the collection of ventilatory parameters). Quantitative variable.

*Lactate: lactate value, from ABG or VBG. Quantitative variable.

*SatvO2: Central venous oxygen saturation. Quantitative variable.

- **Variables related to evolution (2nd phase)**

Exitus: death of the patient between November 21 and December 19. Dichotomous variable yes / no.

Exit date (if applicable): temporary variable.

Extubation date: temporary variable.

UCI discharge: patient discharged from the ICU between November 21 and December 19. Dichotomous variable yes / no.

UCI registration date: temporary variable.

Hospital discharge: patient discharged from the hospital between November 21 and December 19. Dichotomous variable yes / no.

Hospital discharge date: temporary variable.

Statistical analysis:

Once the study has finished, after the registration of the last patient, the database will be closed.

The following proposal is a synthesis of the analytical methodology to be used to provide an answer to the objectives of the research.

All the patients who meet the inclusion criteria will be included in the analysis. Patients who are excluded will be detailed and the reason for their exclusion will be specified.

A general description of the research variables will be made. Absolute and relative frequency distribution of qualitative variables, as well as central tendency and dispersion measures (mean, median, standard deviation, minimum, maximum, interquartile range) of quantitative variables will be submitted. 95% confidence interval (CI) for the main quantitative variables related to the main objective will be also submitted.

Missing data will not be imputed.

If inferential statistics is required, parametric tests wil be used for continous variables and non parametric tests will be used for ordinal, categorical or nonparametric variables.

Statistical test will always be bilateral and with a significance level of 0,05.

For non parametric variables, Mann–Whitney U test (non paired data) or Wilcoxon test (paired data) will be used.

For the analysis of contingency tables as well as for the comparison of proportions and/or frequency distributions, Chi-squared test (or Fisher's exact test when needed) will be used.

To carry out the statistical analysis we count on the support and cooperation of the Department of preventive medicine and public health (Doctors Francisco Javier Llorca Díaz, Trinidad Dierssen Sotos and Inés Gómez Acebo).

Sample size:

The sample size will be determined by the number of participating centres on the date chosen for the cross-section.

Our goal is to enroll at least 2000 patients to estimate the MP that we deliver to patients with greater precision.

Ethical aspects:

The study will be sent to the reference Research Ethics Committee for its approval.

Participating patients will be informed of the aim of the study through a patient information sheet. Patients who agree will be asked to give their informed consent and to sign the informed consent form. If the patient is not able to give consent, the signature of a relative will be required.

Patient rights and security will be guaranteed according to the Declaration of Helsinki (updated in Fortaleza, 2013). Confidenciality of personal data is ensured, in accordance to the basic principles of research ethics and those established by the current legislation (new Organic Law of Data Protection of 25th May 2018, Law 41/2002 of Patient Autonomy, General Health Law 14/1986, Declaration of Helsinki and UNESCO Universal Declaration).

All clinical data that could reveal a patient identification will be processed in the strictest confidence. Paper case report forms and electronic files will not include variables that enable a person identification, according to the new Organic Law of Data Protection of 25th May 2018 and the General Data Protection Regulation (GDPR) EU 2016/679. Data will not be transferred to third parties without the previous consent of the patient or their relatives if the patient cannot give consent.

Administrative and publishing aspects:

All data will be processed in the strictest confidence, according to the Organic Law of Personal Data Protection.

The current study cannot pose a risk for the studied patients because it does not lead to any change in the treatment or in the diagnostic procedures that the patient would undergo under usual clinical conditions.

All information related to the study will be considered confidential until its publication.

The study results will be published in scientific journals and/or through communications to scientific conventions. Members of the executive committee reserve the right to figure as first signatories of the publications that derive from the current study.

The rest of the authors will be considered in decreasing order of their contribution to the study regarding the number of patients included in it, until the maximum number of co-authors allowed by each journal is reached. The researchers who cannot appear as main authors and who have contributed to the study will figure as research collaborators.

With regard to the publishing conditions:

- The study will be published in scientific journals and the corresponding Clinical Research Ethics Committee will be mentioned.
- All cases included in the study will stay anonymous at all times.
- Researchers and coordinators will be in charge of publishing these data or using them for profesional purposes.

Data anonymization and de-identification:

No data that could allow the identification of a patient will be electronically recorded, neither the name nor the date of birth. Name initials and age will be registered and a single identification number generated by the electronic CRF and called ID will be assigned to each patient. Access to the electronic CRF will be provided via e-mail after the enrollment of the healthcare centre.

Data will be safely stored and all procedures related to data management will abide by the Directive 95/46/EC by the European Union on the protection of individuals with regard to the processing of personal data.

Financial disclosure:

The current project is not commissioned by any administration or any public or private company and does not receive any funding.

Only data from usual clinical practice will be registered and, therefore, no additional costs will be incurred by the Hospital.

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Annexes

Annex I. Diagnostic criteria for Acute Respiratory Distress Syndrome (ARDS)

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Acute Respiratory Distress Syndrome The Berlin Definition. JAMA. 2012;307(23):2526-2533
Published online May 21, 2012. doi:10.1001/jama.2012.5669

Annex II. Trademarks of respirators according to whether or not they allow for an inspiratory pause during spontaneous ventilation.

Does not allow for inspiratory pause during PSV	Allows for inspiratory pause during PSV
Getinge – Servo-I	Yes
Getinge – Servo-U	Yes
Getinge – Servo-S	Yes
Draeger – Evita XL	Yes
Draeger – Evita Infinity V500	Yes
GE – Carescape R860	No
Hamilton – G5	Yes
Hamilton – S1	Yes
Medtronic – Puritan Bennet 840	No
Medtronic – Puritan Bennet 980	No
Vyare Medical – Avea	No

Annex III. Method to measure the plateau pressure.

For controlled ventilatory mode: Measure with inspiratory pause of 2-4 sec duration, in cmH2O.

For spontaneous ventilatory mode: those respirators that allow for inspiratory pause on the patient's inspiratory effort (see annex II) will be paused for 2-4 sec in duration. If the ventilator does not allow this inspiratory pause, the P0.1 will be measured (the plateau pressure calculation will be performed by the research team).