ASSESSMENT OF VENTILATORY MANAGEMENT DURING GENERAL ANESTHESIA FOR ROBOTIC SURGERY AND ITS EFFECTS ON POSTOPERATIVE PULMONARY COMPLICATIONS (AVATaR): A prospective observational multicenter study

(NCT02989415)

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ABSTRACT

Introduction: Robotic surgery represents a technological incorporation into minimally invasive surgeries. Despite its growing applicability, the need for pneumoperitoneum and Trendelenburg position in major surgeries significantly affect respiratory mechanics. Considering the growing number of patients submitted to robotic surgery and the implications of anesthesia on the pulmonary pathophysiology, understanding the impact of mechanical ventilation is crucial.

Objective: The aim of this study is to assess the incidence of postoperative pulmonary complications in this group of patients, to characterize current practices of mechanical ventilation during general anesthesia for robotic surgery and to evaluate a possible association between ventilatory parameters and postoperative pulmonary complications.

Study design: This is a prospective observational multicenter study.

Study population: Centers invited to participate will include patients consecutively submitted to mechanical ventilation during anesthesia for robotic surgical procedures during a period of one month.

Main parameters to be studied: The incidence of postoperative pulmonary complications and the effects of the different parameters of mechanical ventilation during general anesthesia in robotic surgery on postoperative pulmonary complications will be investigated for 5 days after surgery or hospital discharge, whichever occurs first.

Nature and extent of the risks associated with participation: Considering the observational nature of the study, there will be no risk to participating patients.

1. INTRODUCTION

1.1. Robotic surgery

Minimally invasive surgery is increasingly being used in recent years (1). Among the possible main advantages of this surgical modality are: 1) reduction in surgical trauma and postoperative pain; 2) low rates of bleeding and need for transfusion; 3) shorter length of stay; and 4) increased patient satisfaction (2). Robotic surgery represents a technological incorporation into minimally invasive surgery and the *da Vinci*© system gathers ergonomy, three-dimensional visualization and magnification of the surgical field, besides great freedom of movement and precision (3). In 2014, the *da Vinci*© system assisted approximately 570,000 surgical procedures in the world, compared to 523,000 and 450,000 in 2013 and 2012, respectively (4). In the USA, 449,000 robotic surgeries were performed; 20% in urology, 52% in gynecology, and 24% in general surgery (4).

Despite the growing applicability of robotic assistance in some surgical modalities, the use of pneumoperitoneum and the head-down (Trendelenburg) position to optimize the surgical field have a marked influence on the patient's respiratory mechanics. Pneumoperitoneum created by CO_2 insufflation causes increased intra-abdominal pressure and cephalic elevation of the diaphragm, promoting a reduction in respiratory compliance and in functional residual capacity (5). Also noted, is increased plateau and peak pressures in more than 50% of patients submitted to pneumoperitoneum, and hypercapnia and reperfusion injury after deflation of the pneumoperitoneum (6,7). The reactive oxygen species, resulting from ischemia-reperfusion injury, can cause damage to distant organs, particularly the lungs (8). Indeed, recent studies suggest that there is a relationship between the pneumoperitoneum and oxidative stress parameters, quantified both in bronchoalveolar lavage and blood. There also may be additional pulmonary inflammation secondary to acidosis that results from CO_2 absorption (9).

A review of 1,500 cases of robotic prostatectomy demonstrated a reduction by 68% in pulmonary compliance that remained even after the end of the pneumoperitoneum (10). Another study describes a reduction by 61% in pulmonary compliance soon after insufflation of pneumoperitoneum and a significant increase in plateau pressure (11). Finally, it was shown that there is an increased upper airway resistance following conclusion of surgery; moreover, in some individuals with no

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prior chronic obstructive pulmonary disease, both tidal volume and forced expiratory volume in 1 second (FEV_1) measured in the postoperative period were reduced, and recovered to normal levels only after five days (12).

1.2. Ventilator-induced lung injury (VILI)

Mechanical ventilation (MV) is an indispensable support for anesthesiologists and intensivists, but it has the potential of aggravating or even causing lung injury (13,14). Hyperdistention of non-dependent areas induced by MV and cyclic opening and closing of dependent pulmonary regions may result in mechanical stress, and eventually, lung injury (15). Lung damage may occur even in a previously healthy organ, and main mechanisms involved are: 1) use of a high tidal volume which can lead to *volutrauma*; 2) the maintenance of high plateau pressures that can generate *barotrauma*; and 3) cyclic opening and closing of alveolar units leading to *atelectrauma*. At cellular level, physical stimulation of mechanical ventilation is transformed into a chemical signal, promoting activation of the immune system with release of pro-inflammatory mediators caused by direct or indirect cellular lesion (16). Ultimately, VILI is the result of a complex interaction among mechanical forces on lung structures such as type I and type II epithelial cells, endothelial cells, macrophages, and extracellular matrix with transformation of the mechanical stimulation into intracellular signaling (17). The sum of these local and immune-mediated phenomena is called *biotrauma* (18).

1.3. Postoperative pulmonary complications

The definition of postoperative pulmonary complications (PPC) includes the development of respiratory events, such as acute respiratory failure, acute respiratory distress syndrome (ARDS), pneumonia, prolonged or unplanned mechanical ventilation, reintubation, hypoxemia, atelectasis, bronchospasm, pleural effusion, pneumothorax, and respiratory depression within a period of 5 to 7 days after surgery (19). Approximately 5% of patients submitted to surgery develop PPC, leading to longer hospital stay and increased mortality rate (20). Major robotic surgeries, associated with pneumoperitoneum, head-down position, and mechanical ventilation have a high potential to cause lung injury and PPC. Recent studies suggest that the use of the protective strategy of MV, combining reduced tidal

volume, low plateau pressure, and application of positive end-expiratory pressure (PEEP) with or without alveolar recruitment maneuvers, is associated with a reduced incidence of PPC in general surgery (21,22).

1.4. Intraoperative mechanical ventilation management

Several studies showed the impact of the protective strategy of MV in reducing PPC in patients submitted to general anesthesia for surgery (21,22). This ventilatory strategy recommends reducing the tidal volume and plateau pressure along with an increase in the PEEP level, and performance of alveolar recruitment maneuvers (23). One observational study conducted in 28 French centers revealed that a large part of patients submitted to general surgery are ventilated without PEEP, and more than 40% of patients are ventilated with a tidal volume > 8 mL/kg (22).

There are no sufficient data in the literature to guide towards the best ventilatory strategy during robotic surgery. This is carried out randomly and according to experience of the anesthesiologist. Mainly, it is believed that ventilatory parameters should be adjusted to maintain normocapnia (24,25). Recently, in a study to evaluate the effects of anesthesia on transperitoneal and extra-peritoneal approaches during robotic prostatectomy, the use of high tidal volumes between 8 to 10 mL/kg was described in order to maintain intraoperative normocapnia (26).

2. OBJECTIVE

<u>Primary objective</u>

To assess the incidence of PPC in patients submitted to robotic surgery.

<u>Secondary objective</u>

To characterize current MV practices during general anesthesia for robotic surgery, and to evaluate the association between MV parameters and intraoperative positioning with the incidence of complications during the intra- and postoperative periods.
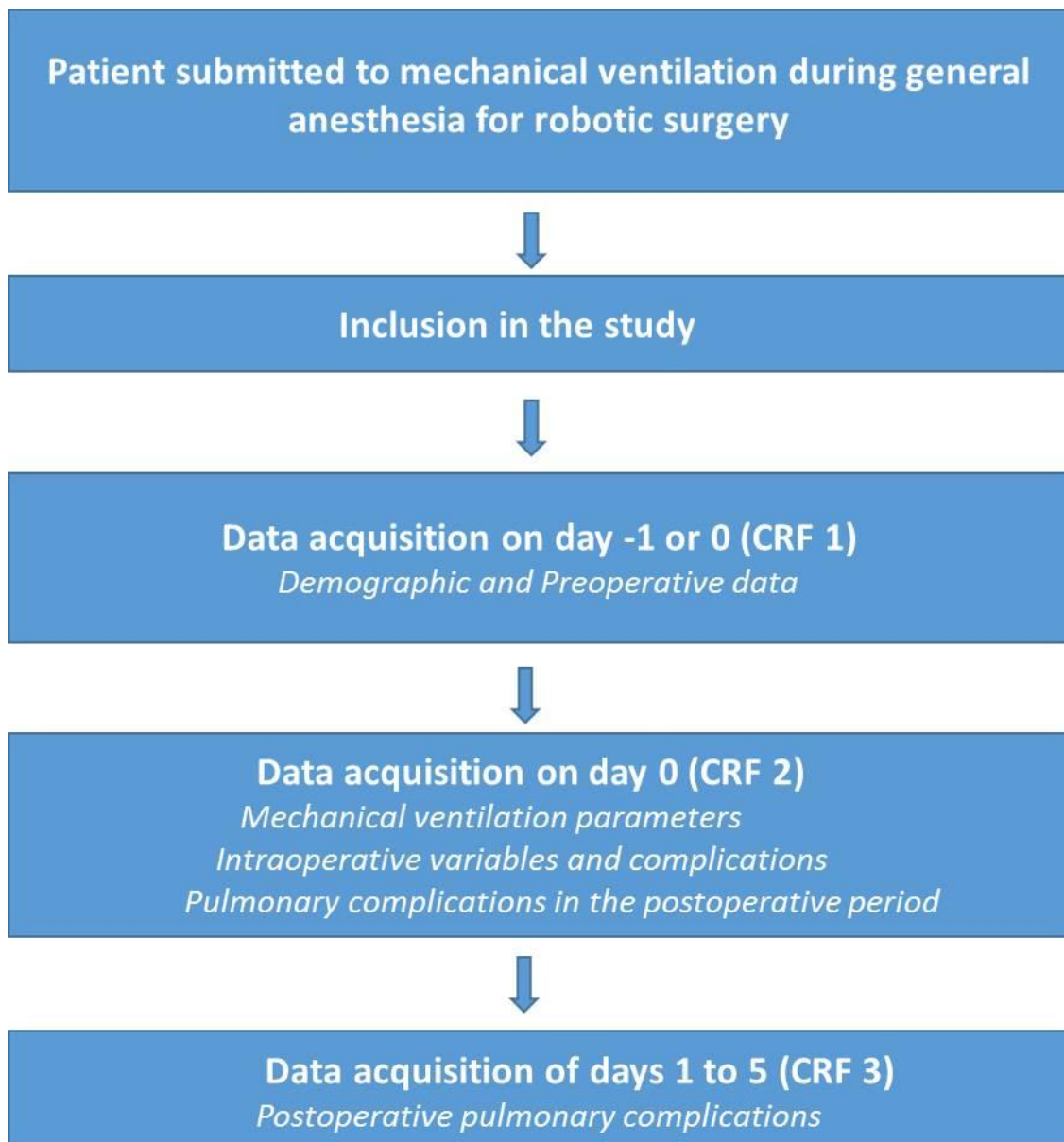
3. STUDY DESIGN

This is a prospective, observational, multinational and multicenter study.

3.1. Study flowchart

Schematic diagram of the study design (procedures and stages):

Patient submitted to mechanical ventilation during general anesthesia for robotic surgery

↓

Inclusion in the study

↓

Data acquisition on day -1 or 0 (CRF 1)
Demographic and Preoperative data

↓

Data acquisition on day 0 (CRF 2)
Mechanical ventilation parameters
Intraoperative variables and complications
Pulmonary complications in the postoperative period

↓

Data acquisition of days 1 to 5 (CRF 3)
Postoperative pulmonary complications

*CRF: Case Report Form

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4. STUDY POPULATION

4.1. Centers and population

Centers with experience and volume in robotic surgery will be invited to participate in the study. Patients submitted to MV during general anesthesia for robotic surgery will be consecutively included during the period of one month.

4.2. Inclusion criteria

- Age ≥ 18 years;
- All surgical procedures performed under general anesthesia for robotic surgery, including head and neck operations, chest, cardiac, and abdominal surgeries.

4.3. Exclusion Criteria

- Any procedure during pregnancy;
- Procedures performed outside of the operating room.

4.4. Calculating the sample size

All patients submitted to MV during general anesthesia for robotic surgery will be consecutively included during the period of one month. No prior sample calculation will be made.

5. METHODS

5.1. Study outcomes

5.1.1. Primary outcome

- Incidence of PPC (defined in Appendix 1) in patients submitted to robotic surgery.

5.1.2. Secondary outcomes

- MV practice in patients submitted to general anesthesia for robotic surgery;
- MV practice according to the risk of PPC;
- Association between MV practice and development of PPC;
- Association between MV practice and development of intraoperative complications;
- Association between surgical positioning and MV parameters;
- Association between insufflation pressure of the pneumoperitoneum and MV parameters;
- Incidence of patients at high risk for PPC (according to the ARISCAT score, defined in Appendix 1) submitted to robotic surgery.

5.2. Randomization

Not applicable.

5.3. Data collection

Data will be collected on a specific electronic Case Report Form (eCRF). Access to the system will be protected by means of the username and password. The following information will be collected for every patient:

5.3.1. Demographic and baseline data

- Date of the informed consent form (if applicable);
- Date of birth, sex, and race (as per the FDA) (27);
- Height and weight (in cm and kg);
- Functional status (independent, partially dependent, or totally dependent);
- Smoking history;

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- Co-morbidities;

- Respiratory infection within the previous 30 days;

- Prior surgery;

- Transfusion of packed red blood cells within 30 days;

- History of MV use in the previous 30 days;

- Expected duration of the operation;

- Surgical procedure;

- Surgical incision (peripheral, abdominal, or thoracic);

- Classification of the surgery (elective, urgency or emergency);

- Preoperative laboratory results (measured no more than 28 days before surgery and if clinically available);

- Peripheral oxygen saturation (SpO_2).

5.3.2. Intraoperative MV parameters and operative times

Ventilatory parameters:

- Ventilatory mode: volume-controlled (VC) or pressure-controlled (PC);

- Peak inspiratory pressure (Ppeak in cmH_2O);

- Plateau pressure, if available (Pplateau in cmH_2O) (definition in Appendix 1);

- Mean airway pressure (Pmean in cmH_2O);

- Tidal volume (V_T in mL);

- PEEP (in cmH_2O);

- Respiration rate (RR per min);

- Fraction of inspired oxygen (FiO_2 in %);

- Use of alveolar recruitment maneuvers (RM) (definition in Appendix 1) (28);

- Peripheral oxygen saturation (SpO_2 in %);

- End-tidal CO_2 ($EtCO_2$ in mmHg or kPa);

- Mean arterial pressure (invasive or non-invasive) (MAP in mmHg);

- Heart rate (HR in bpm).

Operative times used to collect intraoperative ventilatory parameters:

- T1: 5 minutes after anesthetic induction and mechanical ventilation;

- T2: 5 minutes after performance of pneumoperitoneum (when applicable);

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- T3: 5 minutes after surgical positioning for the operation;
- T4: every 60 minutes intraoperatively, which should be divided into T4.1, T4.2, ... T4.10 and so forth successively until the maximum of 10 hours;
- T5: 5 minutes after deflation of the pneumoperitoneum and at the final positioning at the end of the operation.

5.3.3. Intraoperative complications

Events classified as complications during the study:

- Any desaturation (defined as $SpO_2 < 92\%$ for 3 minutes or more);
- Need for previously unplanned RM;
- Need to reduce ventilatory pressure;
- Hypotension (defined as systolic arterial pressure < 90 mmHg or mean arterial pressure < 65 mmHg for 3 minutes or more);
- Need for continuous use of vasoactive drugs (defined in Appendix 1) (29);
- New arrhythmias (defined in Appendix 1) (30).

5.3.4. Perioperative parameters:

- Duration of the anesthetic procedure (in minutes);
- Duration of the surgical procedure (in minutes);
- Respiratory system;
- Type and caliber of the orotracheal tube;
- Association of spinal anesthesia;
- Use of prophylactic antibiotics;
- Monitoring of a neuromuscular blockade;
- Total fluid used in the intraoperative period (crystalloids, colloids, albumin);
- Transfusion of packed red blood cells;
- Hemoglobin at the end of the surgery (if clinically available);
- Temperature at the end of the surgery (in °C or °F);
- Intraoperative positioning (including the record of accentuated Trendelenburg [defined as head-down angulation of 40º (25)]);
- Need to convert from robotic surgery to conventional surgery.

5.3.5. Administration of drugs

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- Use of opioids;
- Use of hypnotics;
- Use of neuromuscular blockers;
- Use of neuromuscular blockade reversal agents.

5.3.6. Postoperative variables

PPC will be collected on Day 0 (end of surgery until 11:59 pm) and on Day 1, 2, 3, 4, and 5 postoperatively (each day goes from 0:00 AM to 11:59 PM). Data collection will be finalized on the day of hospital discharge or on Day 5, if the patient is still hospitalized. If the patient is admitted to the Intensive Care Unit (ICU), the reason for this admission should be documented.

Day 0:

- Residual postoperative curarization (defined as a stimulation rate in the train-of-four [TOF] < 0.9 or clinically diagnosed) (31);
- Invasive mechanical ventilation after discharge from the operating room
    - If yes, specify if the MV was previously planned,
    - If not planned, specify if the ventilatory support was maintained when leaving the operating room or if patient was reintubated;
- Admission to the ICU directly after surgery
    - If yes, specify if the ICU admission was previously planned;
- Pulmonary complications in the postoperative period
    - Need for oxygen therapy (defined as supplementary oxygen used due to PaO_2 < 60 mmHg or SpO_2 < 92% in room air [in individuals with no prior pulmonary disease] or SpO_2 < 88% [in individuals with prior pulmonary disease]). If applicable, record the FiO_2 used (see Appendix 1 for the conversion table),
    - Acute respiratory failure (defined as PaO_2 < 60 mmHg or SpO_2 < 92%, despite treatment with oxygen, or need for non-invasive mechanical ventilation [NIV]). If the NIV was applied, specify the type of interface used (mask or helmet),
    - Pneumonia (defined by the presence of a new or progressive radiographic infiltrate in addition to at least two of the three clinical

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characteristics: fever > 38 °C, leukocytosis or leukopenia [leukocyte count > 12,000 cells/mm or < 4,000 cells/mm³, respectively], and purulent secretion) (32),

- o ARDS (defined as per Berlin Definition) (Appendix 1) (33),
- o Pneumothorax (defined as the presence of air between the visceral and parietal pleura; diagnosis can be made by clinical examination and chest X-Ray) (34).

Days 1, 2, 3, 4, and 5:

- Any new admission to ICU;
- Any new need for MV;
- Development of PPC (definitions above).

6. STATISTICAL ANALYSIS

Collected data are part of the routine clinical care. Patient characteristics will be compared and described by appropriate methods. Student's *t* test or Mann-Whitney's U test will be used to compare continuous variables. Chi-squared or Fisher's exact test will be used for categorical variables. Data will be expressed as mean (standard deviation), median (interquartile interval), and proportion according to what is most appropriate. Comparisons between and within groups will be made using ANOVA and post-hoc analyses for continuous variables. Patients submitted to mechanical ventilation before surgery and those submitted to one-lung ventilation during surgery will be analyzed separately. To identify potential factors associated with intra- and/or postoperative pulmonary complications, univariate and multivariate analyses will be used. The multivariate logistic regression model will be used to identify independent risk factors for pulmonary complications in the postoperative period (35). A gradual approach will be used to introduce new terms to the model, with a limit of *p*< 0.05 to insert the terms. Time variables for the event will be analyzed by means of Cox regression and Kaplan-Meier curve. Statistical significance will be considered as a *p*-value < 0.05. Statistical analyses will be performed using the SPSS software, version 20.0 (SPSS Inc., Chicago, IL) and the R version 2.12.0 (R Foundation for Statistical Computing, Austria).

7. ETHICAL CONSIDERATIONS

7.1. Regulatory bylaws

The study will be conducted according to the principles of the Declaration of Helsinki (version 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMA) (36). Data managing, monitoring, and study reports will be done as per the ICH-GCP Guidelines (37).

7.2 Approval by the Ethical and Regulatory Authorities

All participating centers should present the study to the Institutional Review Board (IRB) for ethical judgment and to obtain a document of proof that the judgment was submitted to revision by IRB and was approved.

7.3. Information for the patient and informed consent form

Consent shall be requested in writing from the patient or his/her legal representative if their clinical conditions do not allow it to be directly obtained from the patient. The request for consent and the information pertinent to the study provided to the patient or to his/her legal representative should be conducted by the investigators of each center or by the study coordinator.

The patient's legal representative and the researcher appointed to obtain the consent should date and sign two copies of the ICF, in which one copy will be given to the patient's legal representative and one copy will be filed with the other study documents. It will be clearly explained to the patients or their legal representatives that their participation in the study is voluntary, and that he/she may withdraw at any time with no implication as to the quality or conduction of subsequent treatment.

The ICF proposed by the study should be evaluated by each research center, and if there is a need for alterations, these should be approved by the Coordinating Center of the Study before submission to the IRB. If the informed consent form is not required by the local IRB, a waiver should be obtained.

The local study coordinator will provide a model of the Informed Consent Form for the participant (see Appendix 2).

7.4. Data confidentiality

The electronic form for data collection will identify the patient and the center investigator by the corresponding number. The data obtained from the medical record should be kept confidential by the researchers, in cabinets with restricted access, and anonymity of all data in temporary and definitive reports will be assured. The data will be treated confidentially and the centers should maintain all data stored for the duration of the study and during the expected time, according to the local rules. After the designated time, the data should be incinerated. All treatment of personal data will comply with the GCP guidelines (37).

8. PUBLICATION AND ADMINISTRATIVE ASPECTS

8.1. Coordinating center

The Coordinating center of the study is *Hospital Israelita Albert Einstein*, São Paulo, Brazil. The responsibilities of the coordinating center include planning and conducting the study, preparation of the protocol, preparation of the case report form (CRF) for data collection, preparation of operating manuals, data management and quality control, statistical analysis, and preparation of the final manuscript.

8.2. Steering Committee

The Steering Committee is responsible for the general supervision of the study, assisting in the development of the study protocol, and preparation of the final manuscript. The members of the Steering Committee are:

- Verônica Neves Fialho Queiroz, MD. Study Coordinator. Physician, resident in anesthesiology at Hospital Israelita Albert Einstein.
- Luiz Guilherme Villares da Costa, MD, PhD. Anesthesiologist of Hospital Israelita Albert Einstein.
- Rogério Póvoa Barbosa, MD. Anesthesiologist of Hospital Israelita Albert Einstein.
- Flávio Takaoka, MD, PhD. Anesthesiologist of Hospital Israelita Albert Einstein.
- Ary Serpa Neto, MD, MSc, PhD. Principal Investigator of the study. Intensivist at the Intensive Care Unit of Hospital Israelita Albert Einstein, São Paulo, Brazil.

8.3. Public disclosure and publication policy

The results of this study will be published in a peer-reviewed medical journal. After the publication of the preliminary results, the set of data gathered will be available to all members that collaborated carrying out secondary analyses, after judgment and approval by the Organizing Committee, regarding scientific quality and validity of the analyses proposed. Before submission, the final version for publication of all manuscripts related to the study should be approved by the Organizing Committee.

8.4. Organization

The national coordinators will be responsible for recruiting centers in their countries and for guaranteeing the appropriate conduction of the study. The local coordinators at each center will provide scientific and structural leadership at their center. They will assure that all local ethical and regulatory approvals necessary are obtained before the beginning of patient inclusion. They will train and accompany their local research group, in order to assure that the study is carried out according to the ICH-GCP orientations (37). Finally, they will guarantee integrity of data collection and inclusion of data in the eCRF.

9. PROPOSED SCHEDULE

	JUL 2016	AUG 2016	SEP 2016	OCT 2016	NOV 2016	DEC 2016	JAN 2017	FEB 2017	MAR 2017	APR 2017	MAY 2017	JUN 2017	JUL 2017	AUG 2017	SEP 2017	OCT 2017	NOV 2017	DEC 2017
Organizing the centers	■	■	■	■	■	■	■											
Ethical approval					■	■	■	■										
Data collection								■	■	■	■	■	■	■	■			
Analyses															■	■		
Preparing the manuscript																■	■	
Submission																	■	■

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10. BUDGET

The project has no sponsors and all expenses will be paid by the researchers.

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37. Guideline for Good Clinical Practice E6(R1). EMEA, (CPMP/ICH/135/95); Jul 2002

APPENDIX 1

1. Definitions

<u>Definition of recruitment maneuvers</u>

When a recruitment maneuver (RM) is performed, the maneuver more closely related to the following definition should be registered:

- *Incremental PEEP*: gradual increase in PEEP with constant tidal volume;
- *Tidal volume recruitment*: gradual increase in tidal volume with constant PEEP;
- *Recruitment combined with PEEP and tidal volume*: PEEP and tidal volume are both gradually increased;
- *Inspiratory pause*: also called CPAP maneuver. During this type of maneuver, a positive pressure in the upper airways greater than 30 cmH_2O is applied for 10 to 30 seconds; and next, it will go back to initial ventilation;
- *Bag insufflation*: manual insufflation with balloon/bag.

<u>Definition of vasoactive drugs</u>

The vasoactive drugs will be taken into account if used differently from what was previously planned. The drugs to be considered are as follows:

- Phenylephrine;
- Vasopressin;
- Dopamine;
- Norepinephrine;
- Epinephrine;
- Dobutamine;
- Ephedrine;
- Atropine;
- Milrinone.

<u>Definition of new arrhythmias</u>

New arrhythmias will be considered if initiated in the intraoperative period and defined as (30):

- Atrial fibrillation (AF): defined by absolute irregularity of R-R intervals and simultaneous loss of P waves in ECG records;

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- Sustained ventricular tachycardia (VT): characterized by ≥ 3 or more consecutives broad QRS complexes with HR > 100 beats/min and duration > 30 seconds;

- Supraventricular tachycardia (SVT): identified as narrow QRS complexes (< 0.12 seconds) with a HR > 180 beats/min;

- Ventricular fibrillation (VF): defined as electrical chaotic ventricular discharge with accentuated variability of morphology, amplification and QRS cycle.

Definition of urgency and emergency surgery

- Emergency: Surgery performed when the patient´s condition is life-threatening;

- Urgency: surgery required within 48 hours;

- Elective: previously scheduled surgery, since it is not an emergency.

Measuring plateau pressure

The plateau pressure shall be measured with an inspiratory pause of at least 0.5 seconds.

Berlin Definition for diagnosis of ARDS

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Time	Within one week of a known clinical insult or worsening of respiratory symptoms
Imaging*	Bilateral opacities not fully explained by pleural effusions, pulmonary or lobar collapse, or nodules
Origin of edema	Respiratory failure not fully explained by heart failure or volume overload. Requires objective evaluation (i.e., echocardiography) to rule out hydrostatic edema, if there are no risk factors
Oxygenation**	
Mild	200 mmHg < PaO_2 / FiO_2 ≤ 300 mmHg with PEEP or CPAP ≥5 cmH_2O***
Moderate	100 mmHg < PaO_2 / FiO_2 ≤ 200 mmHg with PEEP
Severe	100 mmHg ≤ PaO_2 / FiO_2 with PEEP

CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen; PEEP: positive end-expiratory pressure
* chest x-ray or computed tomography
** if the altitude is higher than 1000 meters, the correction factor should be calculated as: [PaO_2 / FiO_2 x (barometric pressure/760)]
*** it can be provided as non-invasive ventilation for mild acute respiratory distress syndrome

Conversion of oxygen therapy from O_2 to FiO_2

Conversion table of oxygen flow to FiO_2

Method	O_2 flow (L/min)	Estimated FiO_2 (%)
Nasal cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6 – 7	50
	7 – 8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

ARISCAT Score

Variables	Risk Score
Age, years	
≤ 50	0
51 – 80	3
> 80	16
Preoperative SpO_2, %	
≥ 96	0
91 – 95	8
≤ 90	24
Respiratory infection in the last month	17
Preoperative anemia (Hb ≤ 10 g/dL)	11
Surgical incision	
Peripheral	0
Upper abdominal	15
Intrathoracic	24
Planned duration of surgery, hours	
≤ 2	0
2 – 3	16
> 3	23
Emergency procedure	8

SpO_2: pulse oximetry breathing room air in supine position; Hb: hemoglobin

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