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# Impact of lung imaging phenotypes on sevoflurane pharmacokinetics and pharmacodynamics during inhaled sedation in patients with acute respiratory distress syndrome: a case-control study. Interim analysis

Oussama Seddiki

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UNIVERSITÉ CLERMONT AUVERGNE

UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

SEDDIKI Oussama

Présentée et soutenue publiquement le 05 octobre 2022

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and pharmacodynamics during inhaled sedation in patients with acute  
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INTERIM ANALYSIS

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# TABLE DES MATIÈRES

REMERCIEMENTS .....	11
TABLE DES MATIÈRES .....	13
LISTE DES TABLEAUX ET FIGURES .....	15
LISTE DES ABREVIATIONS .....	16
BACKGROUND .....	19
METHODS .....	23
<i>Study Design</i> .....	23
<i>Setting</i> .....	23
<i>Eligibility</i> .....	23
Inclusion Criteria .....	23
Non-inclusion Criteria .....	24
<i>Objectives and Endpoints</i> .....	25
Main Objective.....	25
Secondary Objectives.....	25
<i>Intervention</i> .....	25
<i>Blood specimens</i> .....	26
<i>Chromatography</i> .....	27
<i>Statistic</i> .....	28
Sample size estimation .....	28
Data analysis .....	29
<i>Ethical consideration</i> .....	29
RESULTS .....	31
<i>Baseline Characteristics</i> .....	31
<i>Pharmacokinetics of sevoflurane and HFIP</i> .....	32
<i>Secondary objectives</i> .....	32
DISCUSSION .....	38
CONCLUSION .....	42
DECLARATIONS .....	43
<i>Ethics approval and consent to participate</i> .....	43
<i>Consent for publication</i> .....	43
<i>Availability of data and materials</i> .....	43
<i>Funding</i> .....	43
<i>Acknowledgements</i> .....	43
REFERENCES .....	44
CONCLUSION DE THÈSE .....	50

<b>ANNEXES</b> .....	<b>51</b>
<b>SERMENT D'HIPPOCRATE</b> .....	<b>58</b>
<b>SERMENT D'HIPPOCRATE VERSION COURTE</b> .....	<b>59</b>
<b>ABSTRACT</b> .....	<b>60</b>

# LISTE DES TABLEAUX ET FIGURES

## Tableaux

<b>Table 1:</b> Baseline characteristics of the patients	38
<b>Table 2:</b> The bispectral index values, the infusion rates of remifentanyl and renal function during sevoflurane sedation	39
<b>APPENDIX VI:</b> Evolution of sevoflurane and hexafluoroisopropanol plasma concentration	57
<b>APPENDIX VII:</b> Sevoflurane administration features	58
<b>APPENDIX VIII:</b> The evolution of the PaO <sub>2</sub> /FiO <sub>2</sub> ratios	59

## Figures

<b>Figure 1 :</b> The flow diagram of the SPIDERMAN study	32
<b>Figure 2:</b> The pharmacokinetics of sevoflurane	34
<b>Figure 3:</b> The evolution of the plasma concentrations of hexafluoroisopropanol	35
<b>Figure 4:</b> Sevoflurane administration features	36
<b>Figure 5:</b> The evolution of the PaO <sub>2</sub> /FiO <sub>2</sub> ratios	
<b>APPENDIX III:</b> AnaConDa device	54
<b>APPENDIX IV:</b> Timeline of blood samples collection	55
<b>APPENDIX V:</b> Distribution of inclusions	56



## LISTE DES ABBREVIATIONS

**ACURASYS** = The ARDS and Curarisation Systematique study investigators

**ARDS** = Acute Respiratory Distress Syndrome

**BAL** = Broncho Alveolar Lavage

**BiPAP** = Bilevel Positive Airway Pressure

**BMI** = Body Mass Index

**CINC-1**: Cytokine-induced neutrophil chemoattractant protein-1

**CPAP** = Continuous Positive Airway Pressure

**CRF** = Case Report form

**DMSC** = Data Monitoring and Safety Committee

**ECMO** = Extracorporeal Membrane Oxygenation

**EDEN** = Early versus Delayed Enteral Nutrition trial

**EtCO<sub>2</sub>** = End-tidal partial pressure of carbon dioxide

**FACTT** = Fluid and Catheter Treatment Trial

**F<sub>E</sub>sevo** = Expired sevoflurane fraction

**F<sub>I</sub>sevo** = Inspired sevoflurane fraction

**FiO<sub>2</sub>** = Fraction of Inspired Oxygen

**GCS** = Glasgow Coma Scale

**GRADE** = Grading of Recommendations Assessment, Development and Evaluation

**ICU** = Intensive Care Unit

**IL-1 $\beta$**  = Interleukin 1 $\beta$

**IL-6** = Interleukin 6

**IL-8** = Interleukin 8

**IMV** = Intermittent Mechanical Ventilation

**INR** = International Normalized Ratio

**ITT** = Intent to Treat

**KDIGO** = kidney disease improving global outcomes

**LAR** = Legally Authorized Representative

**LTAC** = Long Term Acute Care Facility

**mBW** = Measured Body Weight

**MCP-1**: Monocyte chemoattractant protein-1

**MIP-2**: Macrophage-inflammatory protein-2

**MRC** = Medical Research Council

**NHLBI** = National Heart Lung and Blood Institute

**NIV** = Non-Invasive Ventilation

**NMBA** = Neuromuscular blocking agent

**OSCILLATE** = Oscillation for Acute Respiratory Distress Syndrome Treatment Early

**PaCO<sub>2</sub>** = Partial pressure of arterial carbon dioxide

**PaO<sub>2</sub>** = Partial pressure of arterial oxygen

**PAP** = Pulmonary Artery Pressure

**PB** = Barometric Pressure

**PBW** = Predicted Body Weight

**PEEP** = Positive End-Expiratory Pressure

**PETAL** = Prevention and Early Treatment of Acute Lung Injury

**Pplat** = Plateau pressure

**PP** = Prone Positioning

**PROSEVA** = Proning Severe ARDS Patients study investigators

**PTSD** = Post Traumatic Stress Disorder

**PS** = Pressure Support Ventilation

**RASS** = Richmond Agitation Sedation Scale

**RM** = recruitment maneuver

**SAEs** = Adverse events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure

**SBP** = Systolic Blood Pressure

**SBT** = Spontaneous Breathing Trial

**SC** = Steering Committee

**SOFA** = Sequential Organ Failure Assessment

**SpO<sub>2</sub>** = Oxygen Saturation via pulse oximetry

**SUSAR** = Serious and Unexpected Suspected Adverse Reactions

**TNF- $\alpha$** : Tumor necrosis factor

**VFD** = Ventilator-free Days

**VT** = Tidal volume

## BACKGROUND

The acute respiratory distress syndrome (ARDS) is an acute diffuse and inflammatory lung injury leading to a hypoxemic respiratory failure due to non-cardiogenic pulmonary oedema. ARDS is still an under-recognized challenge for physicians, with a high hospital mortality rate of 35-45% [1]. The current definition of ARDS is the “Berlin definition”, published in 2013, which is defined as bilateral pulmonary opacities on chest radiograph, arterial hypoxemia [partial pressure of arterial oxygen ( $\text{PaO}_2$ ) to fraction of inspired oxygen ( $\text{FiO}_2$ ) ratio  $\leq 300$  with positive end-expiratory pressure (PEEP)  $\geq 5$  cmH<sub>2</sub>O] within one week of a clinical insult or new or worsening respiratory symptoms, with the exclusion of cardiac failure as the primary cause [2]. Despite intense research, the identification of an effective ARDS pharmacologic therapy has failed to date.

Modern-day, volatile agents consist of halogenated agents such as sevoflurane, desflurane and isoflurane. These small fluorinated hydrocarbons possess subtle structural differences that impact their physicochemical properties onset speed, potency, dosing, metabolism and clearance [3]. Their mechanisms of action have been previously described elsewhere [4]. Volatiles have a rapid onset of action, with no significant concerns of drug tolerance or tachyphylaxis [5]. Rapid offset is aided by drug clearance via simple pulmonary exhalation, with low levels of hepatic metabolism (sevoflurane 5%, isoflurane 0.2%, desflurane 0.02%) and production of no significant active metabolites [3]. This contrasts with benzodiazepines, propofol and dexmedetomidine, currently used as intravenous sedation for ICU patients, which rely on adequate hepatic and renal synthetic function for metabolism and clearance.

Volatile halogenated anesthetics such as sevoflurane are widely used to provide general anesthesia in the operating room and they were associated with significant reductions in pulmonary adverse events [6]. Numerous trials now support the efficacy and safety of inhaled

sevoflurane for the sedation of intensive care unit (ICU) patients [7,8]. Sevoflurane is associated with shorter wake-up and extubation times [9,10]. Preclinical studies have shown that inhaled sevoflurane has beneficial effects in experimental ARDS. A first single-center RCT from our group found that early use of inhaled sevoflurane in patients with ARDS is associated with improved oxygenation, reduced levels of some systemic and alveolar pro-inflammatory markers [11].

Volatile anesthetics have been shown in preclinical models to both prevent and minimize the extent of inflammatory lung injury [12,13]. The most commonly proposed mechanism for these effects in various clinical studies and animal models of lung injury including inhaled endotoxin, ventilator-induced lung injury (VILI), sepsis and hemorrhagic shock [6,14] is through a reduction in pro-inflammatory cytokine release. Fortis and colleagues, recently, reported that sevoflurane suppressed pulmonary inflammation in a two-hit experimental model of lung injury (acid instillation and VILI) exerting a lung-protective effect, which is likely mediated by pulmonary GABA<sub>A</sub> receptors [15]. Incubation of human airway epithelial cells with sevoflurane after anoxia reduces the mRNA expression of interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein 1a through an inhibition in the nuclear translocation of nuclear factor kappa beta (NFκB) [16]. In lipopolysaccharide (LPS)-induced ARDS sevoflurane is associated with decreased pulmonary release of inflammatory mediators (TNF- $\alpha$ , CINC-1, MIP-2, MCP-1) (17). Additional work using a rat model of ARDS showed that preconditioning with isoflurane prevents increases in inflammatory mediators found in bronchoalveolar lavage (BAL) samples and reduces histological evidence of lung injury via upregulation of reactive oxygen species in the pre-exposure period [17]. Arguably, the mechanism of this effect could stem from a systemic reduction in inflammation also seen with intravenous anesthetics. However, Ferrando's work in a porcine model of ARDS showed that pre-exposure to sevoflurane results in reduced levels of BAL inflammatory markers and neutrophil cells compared to propofol. Furthermore, this work suggests

a local effect rather than a systemic one [18]. Of note, macrophage-mediated neutrophil migration seems to be attenuated by sevoflurane either in a preconditioning or in a postconditioning setting [19,20]. Recently, a novel pathway of lung protection for volatile anesthetics has been suggested. In a murine model mimicking a patient with ARDS who is then exposed to VILI, Englert's group found that administration of volatile anesthetics during the mechanical ventilation phase reduced the degree of physiologic lung dysfunction not through reductions of inflammatory mediators but rather through preservation of alveolar-epithelial integrity [21]. Taken together, preclinical studies have shown that inhaled sevoflurane improves gas exchange [14,22,23], reduces alveolar oedema and attenuates pulmonary and systemic inflammation in experimental models of ARDS. Interestingly, these effects point out major features that contribute to mortality in ARDS namely impaired lung epithelial function and integrity [24] and phenotypes of severe inflammation [25].

Lung CT-scan shows that there are two morphological phenotypes of ARDS: the nonfocal and focal ARDS [26]. Nonfocal ARDS is defined by diffuse loss of aeration in CT-scan, whereas focal ARDS is defined by predominant aeration loss in lower lobes. Many works show that nonfocal ARDS have worse prognosis [27,28]. In a previous work from our team [11], baseline plasma sRAGE (the soluble form of the receptor for advanced glycation end-products, a marker of epithelial lung injury) values were higher in patients with nonfocal than in those with focal ARDS. However, whether inhaled sevoflurane may have distinct lung-protective effects in focal and nonfocal ARDS remains unknown. When we performed additional analyses to report changes in plasma sRAGE values depending on lung morphology, we found that sevoflurane induced a stronger decrease in plasma sRAGE in patients with nonfocal ARDS suggesting that lung morphology may effectively influence the response to sevoflurane-induced lung-protective effects.

Lung morphology may also influence sevoflurane-induced sedation. In focal ARDS the persistence of normally aerated lung regions may promote sevoflurane diffusion into the

pulmonary circulation. In nonfocal ARDS the loss of lung aeration is diffuse and may impair sevoflurane systemic diffusion [29]. As a consequence, aeration loss may seriously impair sevoflurane systemic diffusion. In a previous work, higher infusion rates of sevoflurane were needed for nonfocal ARDS than for focal ARDS from day 0 to day 1 and from day 1 to day 2, to reach similar expired fractions of sevoflurane, strongly suggesting different patterns of systemic diffusion according to lung morphology in ARDS [30].

These analyses suggest differential responses to sevoflurane in focal and nonfocal ARDS phenotypes, but the impact of lung imaging phenotypes on the effects of sevoflurane and how they may influence sevoflurane-induced sedation during ARDS remains unknown. Due to abnormalities of lung aeration and pulmonary circulation resulting from lung injury, it seems desirable to better characterize sevoflurane pharmacokinetics in ARDS patients requiring mechanical ventilation.

Because we hypothesized that sevoflurane used for inhaled sedation could have distinct pharmacokinetic profiles depending on lung imaging phenotypes (focal versus nonfocal) during ARDS in ICU patients, the SPIDERMAN study protocol (Sevoflurane pharmacokinetics during inhaled sedation relies on the morphotype of ARDS in ICU patients) was designed to assess the sevoflurane pharmacokinetics in ARDS patients requiring mechanical ventilation.

## **METHODS**

### ***Study Design***

The SPIDERMAN study was designed by an investigator-initiated, prospective, case control study. Two groups of patients with moderate-to-severe ARDS were enrolled depending on their morphotype (focal or nonfocal) as routinely assessed in participating centers using CT-scan, chest x-ray and/or lung ultrasound. The patients received inhaled sevoflurane as a standard practice of sedation that is routinely used in participating ICU's. The aim of the SPIDERMAN study was to compare the pharmacokinetic models of sevoflurane-induced sedation during ARDS depending on the lung imaging phenotype (focal versus nonfocal phenotypes).

### ***Setting***

The SPIDERMAN study involved a total of six French centers: three units of the department of perioperative medicine of CHU Clermont-Ferrand, two units of the department of intensive care medicine of CHU Clermont-Ferrand and Saint-Louis hospital Paris and one unit of the department of anesthesiology and critical care medicine of Jean Perrin Comprehensive Cancer Center, Clermont-Ferrand. Each of the six units has strong experience in the management of ARDS patients and mechanical ventilation. The overall implementation of the study was coordinated by the department of perioperative medicine of CHU Clermont-Ferrand.

### ***Eligibility***

#### **Inclusion Criteria**

All adult 18 years patients within 24 hours from meeting the Berlin criteria for moderate or severe ARDS [2] and receiving inhaled sedation with sevoflurane as standard practice will be eligible for inclusion in the study. The 48-hour enrollment time window begins when Berlin criteria are met. Criteria may be met at either the Network or referring hospital. The first qualifying  $SpO_2/FiO_2$  (not the confirmatory  $SpO_2/FiO_2$ ) is used to determine this time window (APPENDIX I).



## Non-inclusion Criteria

The non-inclusion criteria were the lack of informed consent, continuous sedation with inhaled sevoflurane at enrollment, known pregnancy, currently receiving ECMO therapy, chronic respiratory failure defined as  $\text{PaCO}_2 > 60$  mmHg in the outpatient setting, home mechanical ventilation (non-invasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing, body mass index  $> 40$  kg/m<sup>2</sup>, chronic liver disease defined as a Child-Pugh score of 12-15, expected duration of mechanical ventilation  $< 48$  hours, tidal volume of 6 mL/kg predicted body weight (PBW) below 200 mL, decision to withhold life-sustaining treatment, except in those patients committed to full support and cardiopulmonary resuscitation, moribund patient, not expected to survive 24 hours despite intensive care, burns  $> 70\%$  total body surface, previous hypersensitivity or anaphylactic reaction to sevoflurane, medical history of malignant hyperthermia, suspected or proven intracranial hypertension, enrollment in another interventional ARDS trial with direct impact on sedation and PEEP,  $\text{PaO}_2/\text{FiO}_2$  (if available)  $> 200$  mmHg after meeting inclusion criteria and before the start of the study. As oxygenation may improve during the 48-hour enrollment window, this non-inclusion criteria ensures that patients with mild ARDS are not included in the study.

The patients should not be enrolled in another intervention ARDS trial with direct impact on sedation (except the SESAR trial ClinicalTrials.gov Identifier: NCT04235608 [11]). SESAR trial is a prospective and multicentric randomized trial led by our team. The main objective is to assess the efficacy of a sedation with inhaled sevoflurane in reducing mortality and morbidity in patients with moderate-severe nonfocal ARDS in comparison to a control group receiving intravenous sedation.

## ***Objectives and Endpoints***

### **Main Objective**

The primary objective was to compare the pharmacokinetic models of sevoflurane-induced sedation during ARDS depending on the lung imaging phenotype (focal versus nonfocal phenotypes). The primary endpoint was the comparison of the measures of plasma concentration of sevoflurane between focal and nonfocal ARDS at 5 min, 30 min, 1h, 6h, 12h, 24h, and 48h to the detection of sevoflurane (0.1%) by the monitor in the breathing circuit immediately after/and at 5 min, 30 min, 1h, 4h, and 6h after cessation of sevoflurane administration.

### **Secondary Objectives**

The secondary objectives were to report, in patients with focal and nonfocal ARDS, the plasma concentrations of hexafluoroisopropanol (HFIP), a main metabolite of sevoflurane, the fractions of inspired and expired sevoflurane between patients with focal and those with nonfocal ARDS, the infusion rates of sevoflurane needed to reach the target of expired fraction, the bispectral index values, the infusion rates of remifentanyl, the influence of dose and infusion duration of sevoflurane and metabolite on renal function, the evolution of PaO<sub>2</sub>/FiO<sub>2</sub> ratios in focal and nonfocal ARDS. The time-events schedule is reported in APPENDIX II.

### ***Intervention***

In each group, patients received inhaled sedation from the start of the study until sedation can be definitely interrupted or until day 7, whichever occurs first. After day 7, decisions on further use of sedative agents, including type of and dosing of the agent, were as per the treating clinicians. Inhaled sedation with sevoflurane, was vaporized via the miniaturized Anesthesia Conserving Device (AnaConDa-S<sup>®</sup>, Sedana Medical, Uppsala, Sweden) (APPENDIX III) . AnaConDa-S<sup>®</sup> was placed between the endotracheal tube and Y-piece of the ventilator breathing circuit, and sevoflurane was infused into the device for vaporization before inhalation. Sevoflurane infusion rate was adapted from manufacturer's instructions in order to reach a target

of expired sevoflurane fraction ( $F_{E\text{sevo}}$ ) of 0.8-1.1. Inspired sevoflurane fraction ( $F_{I\text{sevo}}$ ),  $F_{E\text{sevo}}$  and expired  $\text{CO}_2$  ( $\text{EtCO}_2$ ) were continuously monitored using a separate bedside gas analyzer. AnaConDa-S<sup>®</sup> has a built-in carbon layer that allows for more than 80% recycling of the expired agent; residual expired gas was scavenged following manufacturer's instructions using an active carbon filter[31].

We will protocolize mechanical ventilation in both arms, based on LIVE study [32]. We will recommend sites to wait at least 16 hours before proning, as in the PROSEVA study [33]. In both groups, patients will receive cisatracurium besylate for neuromuscular blockade [34], and deep sedation will be protocolized to Richmond Agitation-Sedation Scale (RASS) (34) of -4 to -5 before starting, and during, the cisatracurium besylate infusion. The cisatracurium besylate infusion will be continued during 48h and can be stopped if  $\text{PaO}_2/\text{FiO}_2$  exceeds 150 mmHg for 4 hours with  $\text{FiO}_2 < 0.6$  [32,33]; then, light sedation will be targeted (RASS of 0 to -1), with prompt sedation interruption whenever possible. Higher doses of sedation will be allowed for respiratory distress, ventilator dyssynchrony, or hypoxia.

### ***Blood specimens***

The timeline of blood samples collection is summarized in APPENDIX IV. Blood specimens were collected after 5 min, 30 min, 1h, 6h, 12h, 24h and 48h of detection by the monitor of sevoflurane (0.1%) in the breathing circuit and immediately after and at 5 min, 30 min, 1h, 4h and 6h after cessation of sevoflurane administration. At each time, 2 x 2.5 ml, the total blood collected will be 65 ml (2.5 ml x 2 x 13) per patient.

Blood was collected via a venous or an arterial catheter directly into a 2.5 mL vacuum tube, with extreme care being taken to limit residual air. Each sample was promptly centrifuged for 10 min at 1800 rpm. A 1 mL sample of plasma was transferred to a 10 mL headspace chromatography vials screwed hermetically tight with a Teflon-sealed cap (Antélia,

Décines-Charpieu, France), and 10  $\mu\text{L}$  of an internal chromatographic standard solution (600  $\mu\text{g}/\text{mL}$  chloroform in undecane) was added. The tube was immediately and hermetically sealed using a Teflon-sealed cap, frozen at  $-20^{\circ}\text{C}$ , and stored until further analysis (at each pre-specified time point).

As analyses were performed in duplicate, the total blood volume for these draws was a total of approximately 65 mL. Study samples were sent to a central repository (*Centre de Ressources Biologiques Auvergne* (CRB-A), CHU Clermont-Ferrand) to be stored in accordance with good laboratory practices. Samples were identified by a coded number during shipment and storage in the central repository.

### ***Chromatography***

A stock solution of sevoflurane at 50 g/L in methanol and of chloroform (internal standard, IS) at 2 g/L in methanol were prepared. All standard solutions were stored at  $-20^{\circ}\text{C}$ . Then working solutions of sevoflurane at 50, 500, and 5000 mg/L in ultrapure water/dimethyl sulfoxide (50/50; v/v) were prepared. For internal standardization, the working solution was fixed at 100 mg/L in methanol.

The extraction procedure was based on the previously validated method from Bourdeaux and al [35]. A calibration 8-point curve for the concentration ranges of 0.5 – 400 mg/L and multiple quality controls (0.5, 1, 5, 10, 20, 75, 200, and 400 mg/L) was made. Then the samples by spiking 50  $\mu\text{L}$  of IS (100 mg/L) into 1 mL of cellular samples were prepared and sample solutions with 200  $\mu\text{L}$  of saturated sodium chloride water solution, in 10 mL headspace tube screwed hermetically tight with a Teflon-sealed cap were made.

For sample analyses, headspace injections in a gas chromatography coupled with mass detection method (Trace 1310 with TSQ 8000 evo, Thermo Fisher Scientific, San Jose, CA, USA) were used. After 10 min at  $80^{\circ}\text{C}$  with agitation, 1.5 mL of gas sample was put in the gas chromatograph. Injector was carried over at  $260^{\circ}\text{C}$  with a split flow at 100 mL/min during 2 min.

Split / splitless injector used a carrier mode-programmed pressure. First, the gas pressure were kept at 40 kPa during 0.15 min. Then, the rate program pressure was increased to 150 kPa at 125 kPa/min before a rate of 16 kPa/min to 300 kPa pressure was set for 5 min. Simultaneously with the injection, an oven temperature of 60°C was started during 1 min and was increased until the temperature of 140°C will be reached at the rate of 20°C/min. Then, a second increase was applied until 250°C. The total time of the run was 7 min.

Chromatography separation was carried out using a Rxi-624Sil MS column (30 m x 1.4 µm, 0.25 mm ID) (Restek, Lisses, France). Mass experiments were performed with a single ion monitoring (SIM) condition, and ion quantification m/z 181, and ions qualifications m/z 151 and 51 were simultaneously monitored at retention time (RT) 2.30 min for sevoflurane, and m/z 83 (ion quantification) for chloroform at RT 3.70 min. The concentration of sevoflurane was determined by their area ratios to that of the IS using a weight quadratic fit. Lower limit of quantification (LLOQ) for sevoflurane was at 0.5 mg/L and upper limit of quantification (ULOPQ) was at 400 mg/L in sample.

## *Statistic*

### **Sample size estimation**

To propose a robust sample size estimation is difficult because both the between- and within-patient variabilities are unknown. However, considering the scientific literature, several papers such as Ogungbenro K. and Aarons L.[36–42] report a range of population from 12 to 20 patients to design robust and efficient pharmacokinetic studies with a statistical power greater than 80%. Consequently, we will include a total of 2 x 20 patients with an interim analysis planned after 2 x 10 patients.

Furthermore, on the basis of a previous work of Kang et al. based on simulation-process such as Markov Chain Monte Carlo methods, a total of 40 patients with five repeated values allowed to study the pharmacokinetic of sevoflurane with minimal difference between groups

equals 0.5 with a two-sided type I error at 5%, a statistical power of 90% and an interclass correlation coefficient (ICC) of 0.5. With 20 patients and the same statistical hypothesis, the minimal difference between groups will equal 0.8.

### **Data analysis**

The categorical variables are described by numbers and percentages and the quantitative variables by the mean and the standard deviation or the median and the interquartile deviation with regard to their statistical distribution. Normality (study of Gaussian character) was examined by the Shapiro-Wilk test. The evolution of the repeated data (including sevoflurane concentration) was analyzed by mixed linear models making it possible to model inter- and intra-patient variability (subject effect considered to be random). The normality of the residuals was studied by Shapiro-Wilk test and graphical visualization. Where appropriate, a logarithmic transformation of the dependent variable under study has been proposed. Subgroup analysis by focal and nonfocal trait considered the same statistical approaches; the time x group (focal and non-focal) interaction was studied. All analyzes were performed with Stata® software (version 15, StataCorp, College Station, USA). The risk of type I error was set at 5% (bilateral); a Sidak-type correction was applied for multiple comparisons in the repeated data analysis.

### ***Ethical consideration***

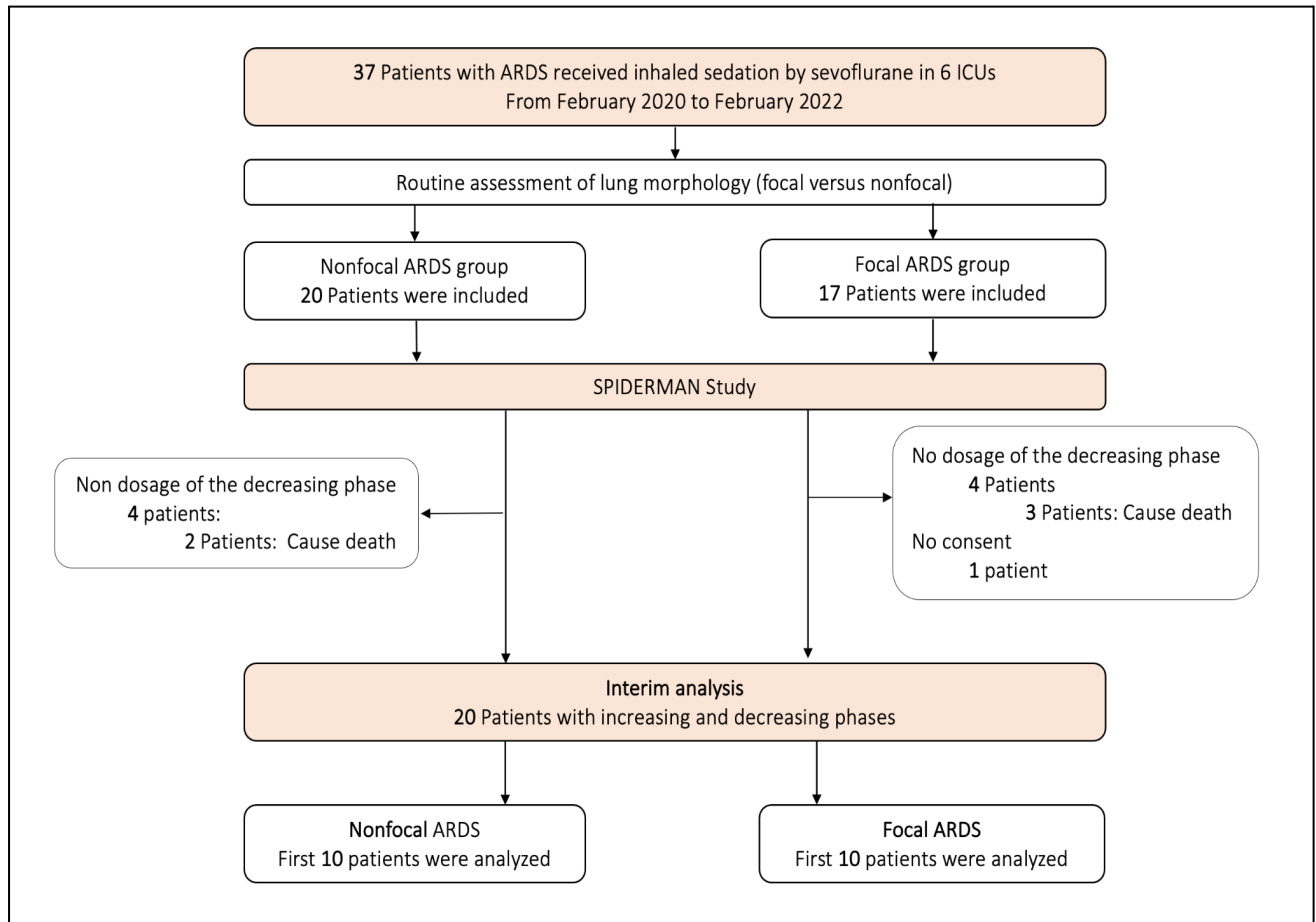
The SPIDERMAN study was conducted in accordance with the Declaration of Helsinki and has been registered at <http://www.clinicaltrials.gov> on July 17, 2019 with identification number NCT04023305. The study protocol was approved by the ethics committee *CPP Ile de France VIII* and the ANSM in May 2019 (approval number N°EudraCT\_2018\_003511\_21).

Because patients with ARDS were very likely to receive deep sedation and invasive mechanical ventilation (or to need emergent tracheal intubation and invasive mechanical ventilation if not already the case), they were very likely to lack capacity to provide informed consent when eligible to enrolment into the study and the study protocol provided for a waiver of informed consent from the patient. In addition, because in emergency situations, sedation and

ventilation must be initiated as early as possible, the study protocol implied a short enrollment time window of 48 hours since ARDS Berlin criteria were met. Therefore, and because the consent from the patient's next of kin was less likely to be obtained during this short time window, the investigator decided to include the patient in the study using an emergent consent procedure; no consent from the patient's next of kin was required, but the investigator informed the patient's next-of kin of his/her decision to include the patient in the study whenever possible. Deferred informed consent was obtained as soon as possible from participants for potential continuation of the research.

## RESULTS

The flow of the participants through the study is shown in **Figure 1**.



**Figure 1** : The flow diagram of the SPIDERMAN study.

### *Baseline Characteristics*

A total of 37 patients of the inclusions have been included in the study to date. Inclusions by center and rhythm are presented in Appendix V. The study is currently in progress; in this work, we present an intermediate analysis of 20 patients. The baseline characteristics of the patients are reported in **Table 1**. Pneumonia was the most common cause of ARDS. At the inclusion, ARDS severity, as assessed by  $\text{PaO}_2/\text{FiO}_2$  ratios, was  $111 \pm 49$  mmHg in the nonfocal group compared to  $144 \pm 57$  mmHg in the focal group.



## *Pharmacokinetics of sevoflurane and HFIP*

The plasma concentrations of sevoflurane over time are shown in **Figure 2**, for which no significant difference was observed between the focal and nonfocal ARDS groups. The plasma concentrations of HFIP are shown in **Figure 3**, and no significant difference was found between the focal and nonfocal groups, except in T3 and T9. The value plasma concentration of HFIP is shown in Appendix VI.

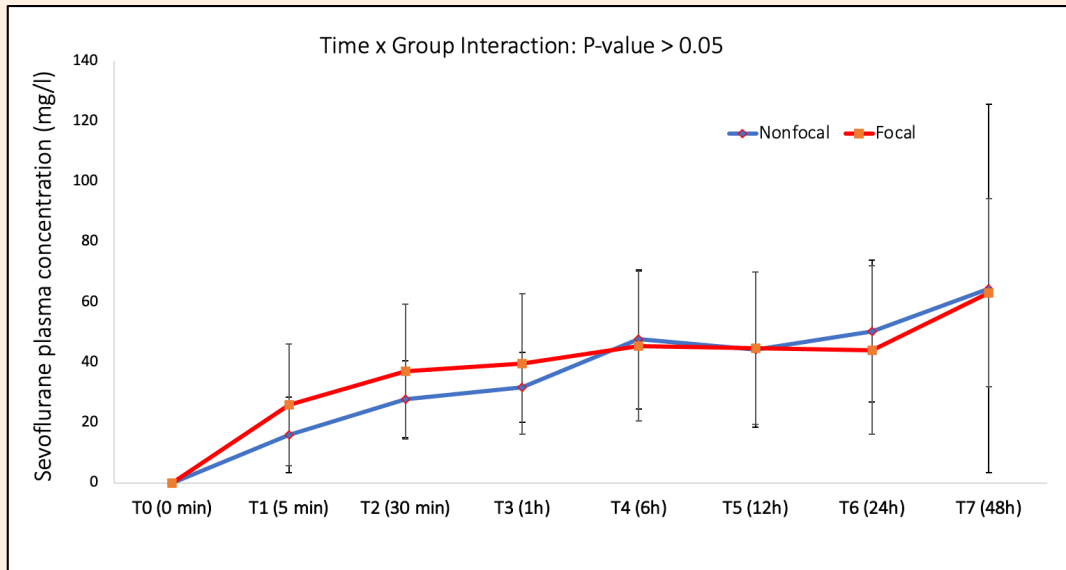
## *Secondary objectives*

The infusion rates of sevoflurane,  $F_{I\text{sevo}}$ , and  $F_{E\text{sevo}}$  are reported in **Figure 4**. No significant differences were observed between the focal and nonfocal ARDS groups, except in T8, where the infusion rate of sevoflurane was significantly higher in the nonfocal group ( $5.2 \pm 4.6$ ) than in the focal group ( $1.45 \pm 2.2$ ) ( $P = 0.03$ ). Furthermore, the end-expiratory fraction of sevoflurane was significantly different ( $1.39 \pm 1$  in the nonfocal group compared to  $0.76 \pm 0.31$  in the focal group;  $P = 0.01$ ), as shown in Appendix VII.

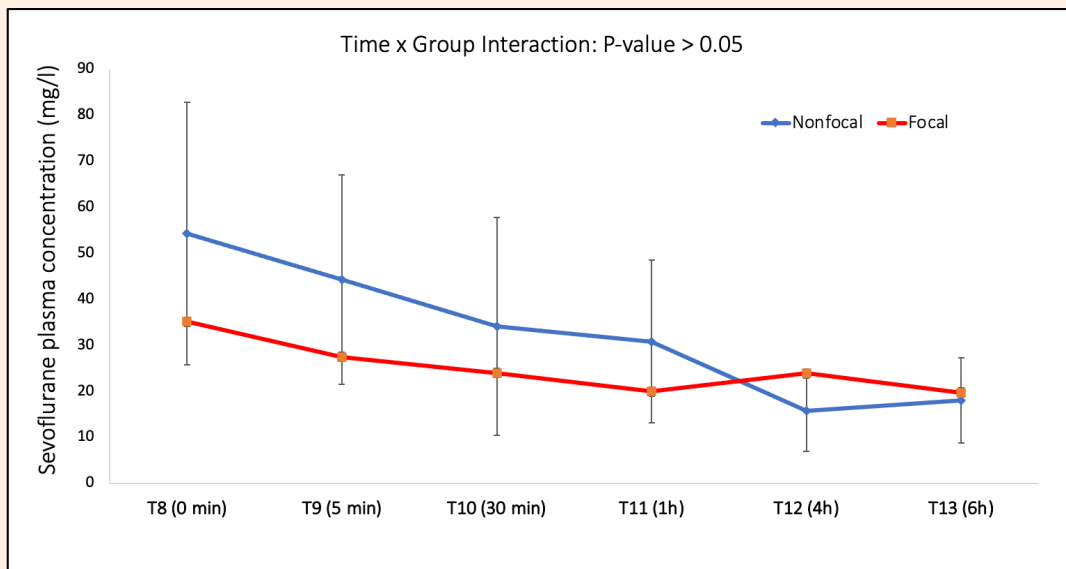
The bispectral index and renal function during inhaled sedation are reported in **Table 2**. No significant differences were observed between the focal and nonfocal ARDS groups.

The infusion rate of remifentanyl is reported in **Table 2**. No significant differences were observed in the nonfocal and focal ARDS patients 48 h after the initiation of inhaled sedation. However, 6 h after the cessation of sedation, the infusion rate of remifentanyl was significantly higher in the nonfocal group compared to the focal group from T9 to T12.

Evolution of the  $\text{PaO}_2 / \text{FiO}_2$  ratios are reported in **Figure 5**.  $\text{PaO}_2 / \text{FiO}_2$  ratios in nonfocal patients were significantly lower than  $\text{PaO}_2 / \text{FiO}_2$  ratios in focal patients at tow times: T8 ( $139 \pm 34.88$  in the nonfocal group versus  $221 \pm 82.9$  in focal group;  $P = 0.02$ ) and T12 ( $131 \pm 30$  in nonfocal group versus  $209 \pm 62.33$  in focal group;  $P = 0.04$ ) (APPENDIX VIII).

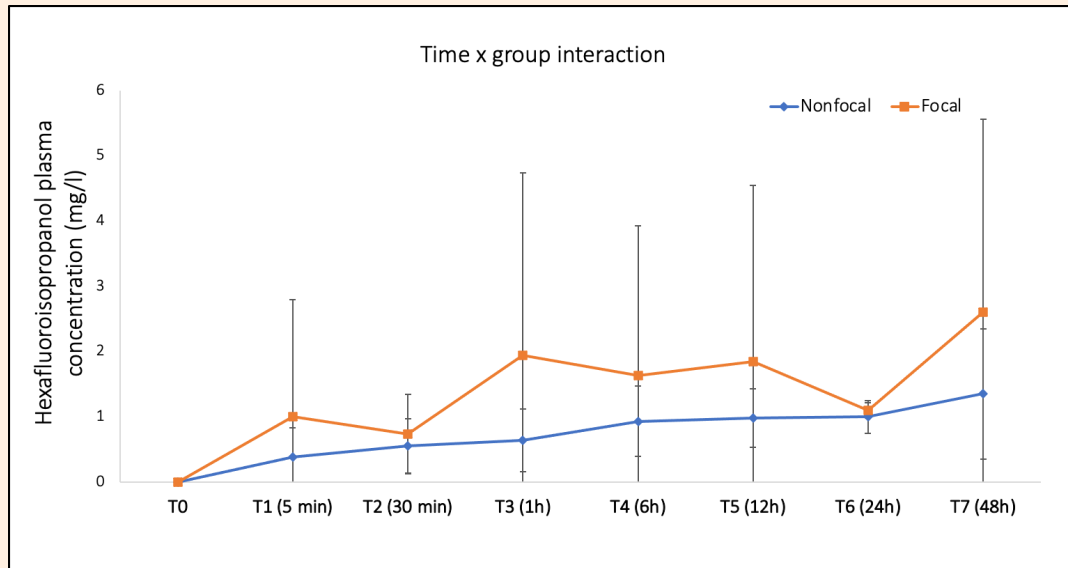


**Figure 2-A:** The plasma concentration of sevoflurane from the initiation of inhaled sedation up to 48 hours. Results are expressed as means  $\pm$  SD.

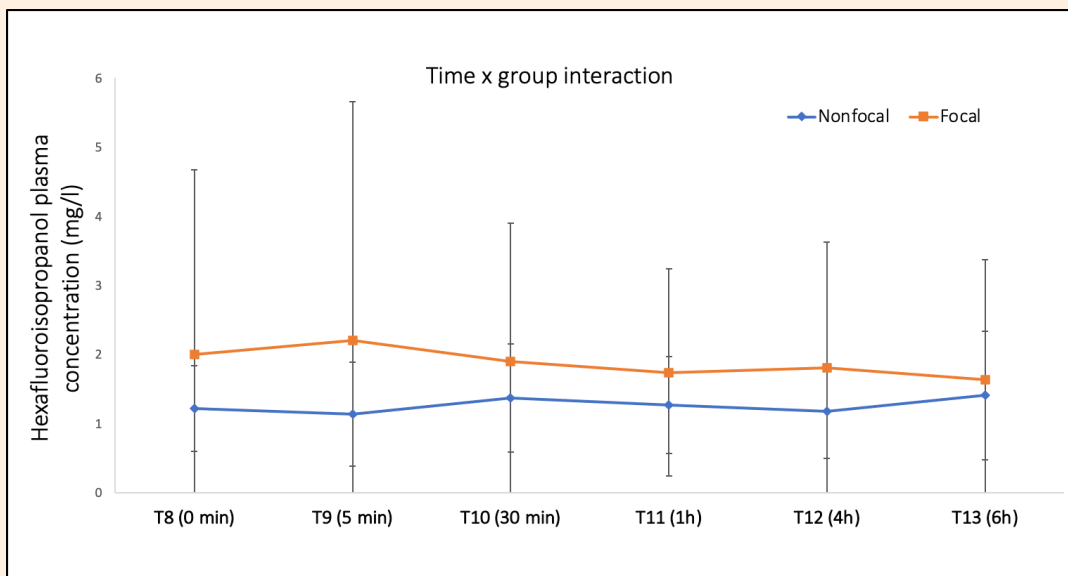


**Figure 2-B:** The plasma concentration of sevoflurane from the cessation of inhaled sedation up to 6 hours. Results are expressed as means  $\pm$  SD.

**Figure 2:** The pharmacokinetics of sevoflurane in nonfocal and focal ARDS from the initiation to the cessation of inhaled sedation. Details of statistical data in each time are reported in APPENDIX VI.

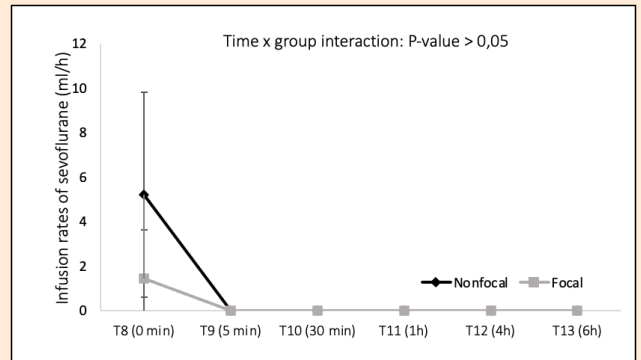
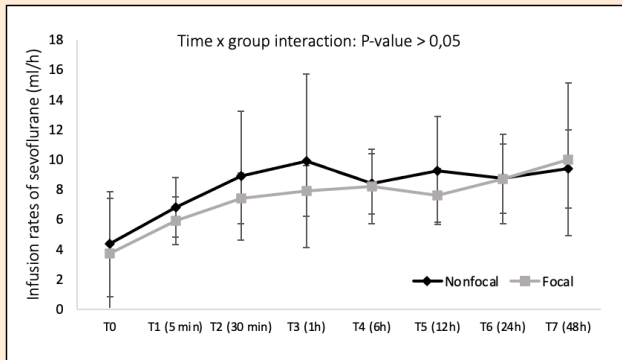


**Figure 3-A:** The evolution of the plasma concentration of hexafluoroisopropanol from the initiation of inhaled sedation up to 48 hours. Results are expressed as means  $\pm$  SD.

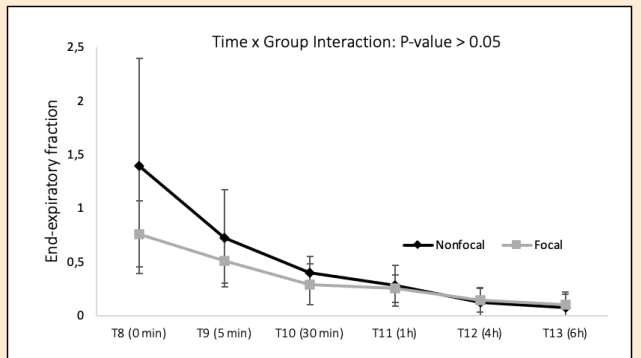
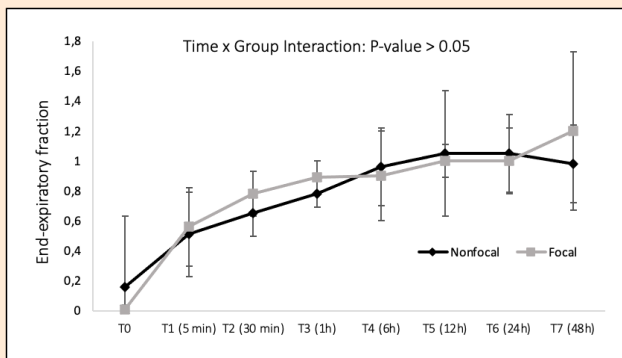


**Figure 3-B:** The evolution of the plasma concentration of hexafluoroisopropanol from the cessation of inhaled sedation up to 6 hours. Results are expressed as means  $\pm$  SD.

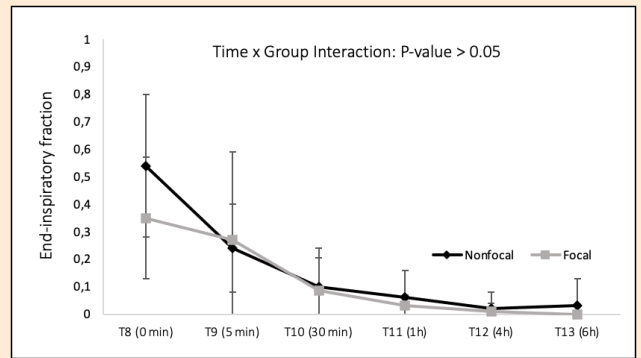
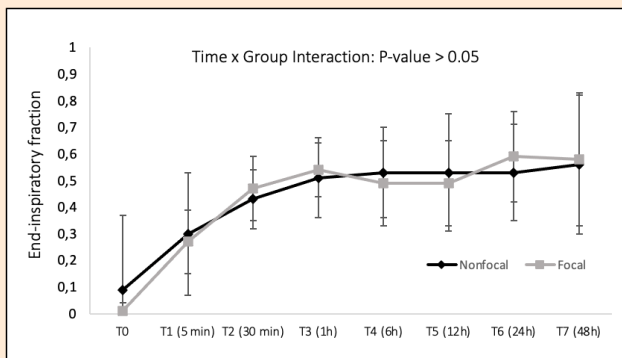
**Figure 3:** The evolution of the plasma concentrations of hexafluoroisopropanol in nonfocal and focal ARDS from the initiation to the cessation of inhaled sedation. Details of statistical data in each time are reported in APPENDIX VI.



**Figure 4-A:** Infusion rates of sevoflurane (ml/h) in nonfocal and focal ARDS during 48 hours from initiation of inhaled sedation (left) and during 6 hours from cessation sedation (right). Results are expressed as means  $\pm$  SD.

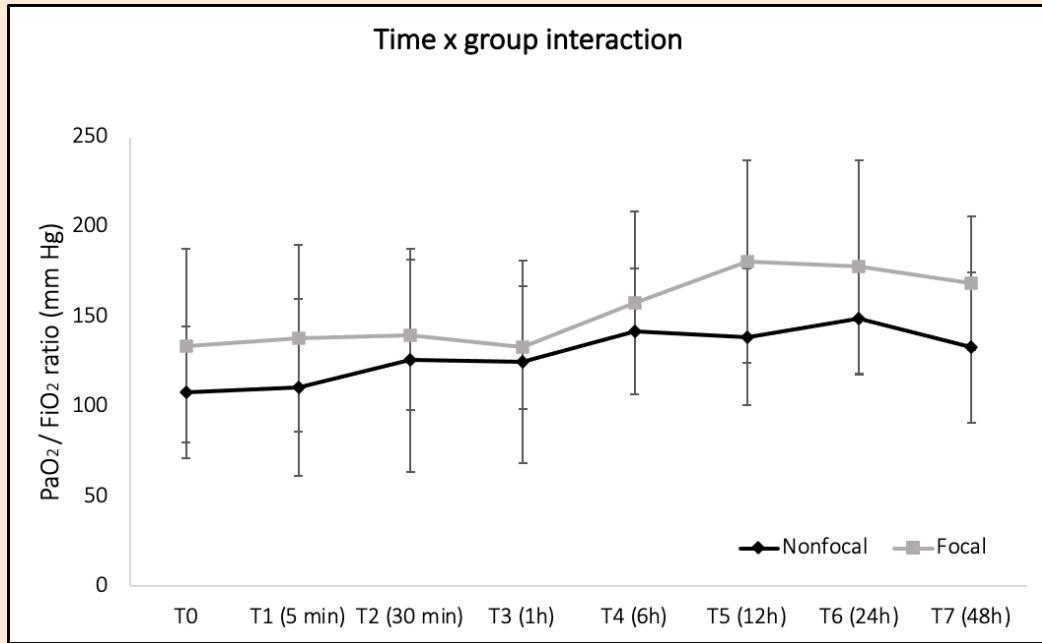


**Figure 4-B:** End-expiratory fraction of sevoflurane ( $Fe_{SEVO}$ ) in nonfocal and focal ARDS during 48 hours from initiation of inhaled sedation (left) and during 6 hours from cessation sedation (right). Results are expressed as means  $\pm$  SD.

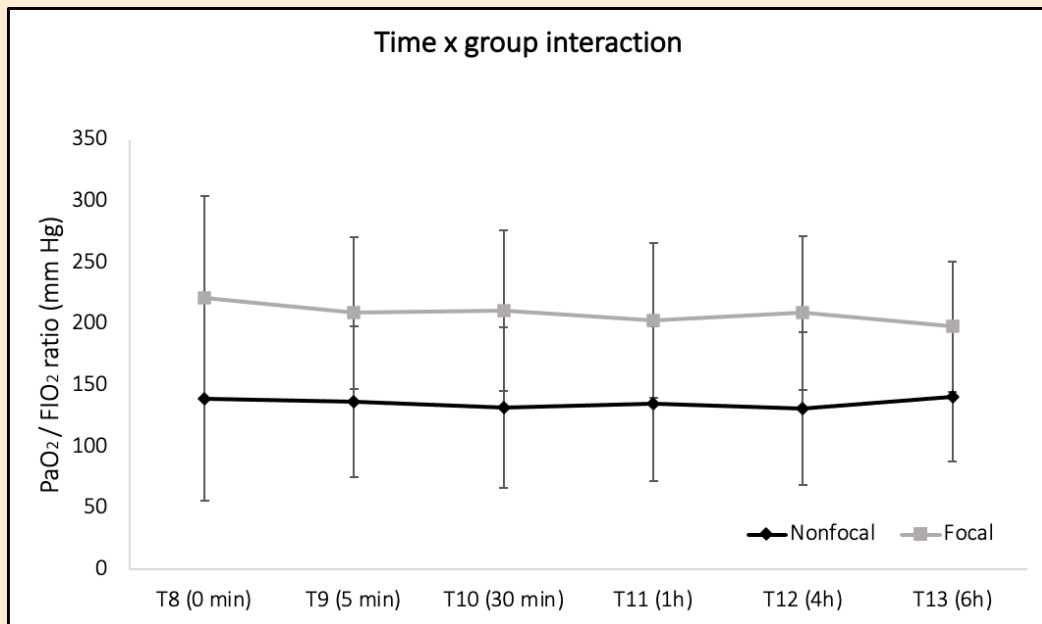


**Figure 4-C:** End-inspiratory fraction of sevoflurane ( $Fi_{SEVO}$ ) in nonfocal and focal ARDS during 48 hours from initiation of inhaled sedation (left) and during 6 hours from cessation sedation (right). Results are expressed as means  $\pm$  SD.

**Figure 4:** Sevoflurane administration features: infusion rate, end-expiratory fraction and end-inspiratory fraction in nonfocal and focal ARDS groups.



**Figure 5-A:** The evolution of the PaO<sub>2</sub>/FiO<sub>2</sub> ratios from the initiation of inhaled sedation up to 48 hours. Results are expressed as means ± SD.



**Figure 5-B:** The evolution of the PaO<sub>2</sub>/FiO<sub>2</sub> ratios from the cessation of inhaled sedation up to 6 hours. Results are expressed as means ± SD.

**Figure 5:** The evolution of the PaO<sub>2</sub>/FiO<sub>2</sub> ratios in nonfocal and focal ARDS during inhaled sedation. Details of statistical data in each time are reported in APPENDIX VIII.

**Table 1: Baseline characteristics of the patients**

Characteristic	Nonfocal group (N=10)	Focal group (N=10)
Age - years	63 ± 15	70 ± 9
Body-mass index	28 ± 5	27 ± 5
Setting from which patient was admitted to ICU, n/total		
Emergency room	5/10	2/10
Home	2/10	1/10
Medicine	2/10	2/10
Surgery	1/10	3/10
Other	0/10	2/10
Medical history, n (%)		
Hypertension	4 (40)	6 (60)
Diabetes	2 (20)	4 (40)
Chronic obstructive pulmonary disease	1 (10)	1 (10)
Active solid cancer	1 (10)	0 (0)
Malignant hemopathy	0 (0)	0 (0)
Immunosuppression	1 (10)	0 (0)
Alcohol dependence	0 (0)	1 (10)
Active tobacco smoking	2 (20)	2 (20)
Knaus score at admission, n (%)		
A	6 (60)	5 (50)
B	3 (30)	5 (50)
C	1 (10)	0 (0)
D	0 (0)	0 (0)
Mac Cabe Scale at admission, n (%)		
1	9 (90)	9 (90)
2	1 (10)	0 (0)
3	0 (0)	1 (10)
Type of ICU admission, n (%)		
Medical	9 (90)	5 (50)
Surgical	1 (10)	5 (50)
SOFA at admission (from 0 to 24)	6 ± 3	6 ± 3
SAPS II at admission	52 ± 16	48 ± 17
Acute renal failure KDIGO at inclusion, n (%)		
No	7 (70)	7 (70)
1	1 (10)	2 (20)
2	1 (10)	1 (10)
3	1 (10)	0 (0)
Assessment of ARDS morphology, n (%)		
CT-Scan	10 (100)	10 (100)
Radiography	0 (0)	0 (0)
Ultrasound	0 (0)	0 (0)
Cause of ARDS, n (%)		
COVID-19 pneumonia	2 (20)	1 (10)
Bacterial pneumonia	5 (50)	7 (70)
Chest trauma	1 (10)	0 (0)
Others	2 (20)	2 (20)
Mechanical ventilation before inclusion, n (%)	2 (20)	5 (50)
FiO <sub>2</sub> at inclusion, (%)	77 ± 20	60 ± 19
PaO <sub>2</sub> /FIO <sub>2</sub> ratio at inclusion, (mmHg)	111 ± 49	144 ± 57
PaCO <sub>2</sub> at inclusion, (mmHg)	50 ± 5	41 ± 5

Definition of abbreviations: SAPS II: Simplified Acute Physiologic Score. KDIGO : Kidney Disease Improving Global Outcomes. COVID-19: CoronaVirus Disease appeared in 2019. Knaus score: A: normal health; B: moderate limitation; C: important limitation; D: bedridden patient, major restriction. Mac Cabe Scale: 1 = No deadly disease; 2 = Fatal illness at 5 years; 3 = Fatal disease at 1 year. Data are presented as mean ± SD.

Parameters	Nonfocal Mean ± SD	Focal Mean ± SD	Time x group interaction P-value
<b>Bispectral index (BIS)</b>	<b>(N=8)</b>	<b>(N=6)</b>	
T0 (Start sevoflurane)	60.14 ± 18.23	42.16 ± 9.49	--
T1 (5 min)	55.42 ± 20.46	44.33 ± 9.33	0.21
T2 (30 min)	48 ± 9.48	39 ± 6.67	0.42
T3 (1h)	51.75 ± 11.43	39.33 ± 6.31	0.51
T4 (6h)	56.42 ± 8.63	41.33 ± 4.41	0.36
T5 (12h)	62.37 ± 19.01	49.16 ± 17.04	0.08
T6 (24h)	54.5 ± 12.88	46.6 ± 8.17	0.09
T7 (48h)	43 ± 19.58	42.8 ± 13.93	0.45
T8 (0 min, stop Sevoflurane)	46.75 ± 3.59	52 ± 20.41	0.44
T9 (5 min)	57 ± 15.23	55.5 ± 24.14	0.12
T10 (30 min)	59.25 ± 9.53	65 ± 21.74	0.52
T11 (1h)	54 ± 5.29	69.75 ± 16.93	0.86
T12 (4h)	51 ± 7	69.25 ± 19.15	0.63
T13 (6h)	46.5 ± 3.53	76.25 ± 12.65	0.12
<b>Remifentanil infusion rate (ml/h)</b>	<b>(N=9)</b>	<b>(N=10)</b>	
T0 (Start sevoflurane)	5.3 ± 4	5.3 ± 1.5	--
T1 (5 min)	5.7 ± 3.5	5.3 ± 1.5	0.70
T2 (30 min)	5.8 ± 2.3	5.2 ± 1.6	0.70
T3 (1h)	6.2 ± 3	5.2 ± 1.5	0.39
T4 (6h)	6.3 ± 3.7	5 ± 1.8	0.25
T5 (12h)	5.8 ± 3.4	5.3 ± 2	0.63
T6 (24h)	5.8 ± 3.7	4 ± 2.3	0.11
T7 (48h)	5.7 ± 3.4	5 ± 3.4	0.68
T8 (0 min, stop Sevoflurane)	7.12 ± 3.4	4.7 ± 1.9	0.05
T9 (5 min)	7.25 ± 3.5	4.4 ± 2.1	0.02
T10 (30 min)	7.25 ± 3.5	4.2 ± 2.6	0.01
T11 (1h)	6 ± 4.2	4.1 ± 2.9	0.03
T12 (4h)	6.37 ± 4.1	3.7 ± 2.7	0.03
T13 (6h)	6.12 ± 4	3.8 ± 2.8	0.06
<b>Glomerular filtration rate (ml/min/1.73 m<sup>2</sup>)</b>	<b>(N=10)</b>	<b>(N=10)</b>	
T0 to T4	71 ± 40	61 ± 36	0.90
T5	63 ± 37	60 ± 38	0.50
T6 to T7	61 ± 41	63 ± 38	0.18
T8 to T13	65 ± 34	65 ± 33	0.30

**Table 2:** The bispectral index values, the infusion rates of remifentanil and renal function during sevoflurane sedation. The glomerular filtration rate was calculated by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). Results are expressed as means ± SD.

## DISCUSSION

This study is the first to analyze the pharmacokinetics of sevoflurane, depending on the lung morphology of ARDS. In this interim analysis, sevoflurane inhaled for sedation did not present distinct pharmacokinetic profiles depending on lung imaging phenotypes (focal versus nonfocal) during ARDS in ICU patients.

ARDS is a frequent and deadly condition associated with greater healthcare utilization, reduced quality of life and worse long-term physical and cognitive outcomes among survivors. Despite intense research, no effective ARDS therapy is available to date. Numerous trials support the efficacy and safety of volatile anesthetic agent sevoflurane through dedicated devices for the sedation of ICU patients, with superior awakening and extubation times in comparison with intravenous sedatives such as propofol or benzodiazepines. In addition, sevoflurane may possess important end-organ protective properties mediated via cytoprotective and anti-inflammatory mechanisms that are very relevant to the pathogenesis and resolution of ARDS. Preclinical studies have shown that inhaled sevoflurane improves gas exchange, reduces alveolar oedema, and attenuates pulmonary and systemic inflammation in experimental models of ARDS. Such beneficial effects of sevoflurane on oxygenation, inflammation, and lung epithelial injury in ARDS were recently confirmed in a first, single-center randomized controlled trial from our group [11].

We initially hypothesized a difference in the pharmacokinetics of sevoflurane according to the morphology focal versus nonfocal of ARDS. The difference in residual loss-aeration between these two morphotypes, higher in the nonfocal type, suggests probably greater and faster lung absorption and elimination in focal ARDS. In this interim analysis, even if no difference was observed during the initiation phase of sevoflurane, the kinetics of sevoflurane plasma levels were lower in the focal patients compared to nonfocal patients. These kinetics were associated to the



depth of sedation reported by the BIS-value in both groups, nevertheless this difference was not statistically significant, possibly related to the lack of power due to the analysis on the first 20 patients. In our interim analysis, we observed that remifentanyl administration rates were significantly lower in the focal versus non-focal group upon cessation of sevoflurane sedation from T9 through T12.

However, recent analyses suggest different responses to sevoflurane in focal and nonfocal ARDS phenotypes [29,43], but the impact of lung imaging phenotypes on the effects of sevoflurane and how they may influence sevoflurane-induced sedation during ARDS remains unknown. Due to abnormalities of lung aeration and pulmonary circulation resulting from lung injury, it was necessary to better characterize sevoflurane pharmacokinetics in ARDS patients requiring mechanical ventilation. Unlike previously suggested, the morphology of lung injury does not seem to impact neither the plasma concentration of sevoflurane nor the level of sedation assessed in part by the BIS value. This study allows investigating specific ARDS phenotypes (morphology of lung injury, focal versus nonfocal) and their specific response to sevoflurane (ARDS endotypes) to ultimately enrich future trials and inform future strategies of personalized ARDS medicine.

Interestingly, initiation of the inhaled sedation was associated with an improvement of the oxygenation as assessed by an increase of the  $\text{PaO}_2/\text{FiO}_2$  ratios. Similar results were found in a previous study of our group [11]. Nevertheless no difference in the improvement was found between the focal and nonfocal patients. In this study, patients with focal morphology of ARDS had higher  $\text{PaO}_2 / \text{FiO}_2$  ratios than nonfocal patients that probably reflect the severity of the lung injury. Even if no difference were found in the gas exchange parameters between the nonfocal and focal ARDS in a prospective multicenter cohort study involving 119 consecutive patients [28], patients with nonfocal ARDS had higher plasma levels of the receptor for advanced glycation

end-products (RAGE), a biomarker of the epithelial injury. Unfortunately, the plasma levels of RAGE have not been measured in this study.

Regarding HFIP, a metabolite of sevoflurane, eliminated by the kidney, we did not observe a statistically significant difference in the kinetics of the HFIP metabolite in the focal versus non-focal group. With the exception of T3 (1h) and T9 (5 min of stopping sevoflurane) the level of HFIP was significantly higher in the focal versus nonfocal group. Renal function was comparable in the two groups. No impact of sevoflurane sedation was observed on the evolution of renal function in the two groups. A potential risk during long-term sedation is a change in metabolism of the gas and/or HFIP in plasma. Accumulation of the sedative or saturation of the cytochrome P450 E2 biotransformation process may occur [44]. Saturation of conjugation of HFIP with glucuronic acid prior to urinary elimination might also take place thus raising the free HFIP concentration and creating a potentially toxic effect. The morphology of lung injury during ARDS did not seem to influence the plasma concentration of HFIP in our study suggesting that the morphology of lung injury has no impact on the potentially toxic effect of sevoflurane. Furthermore, the same results were found about renal failure. Indeed, no significant difference was found for the glomerular filtration rate between nonfocal and focal patients.

This study occurs in a personalized strategy for ARDS according to the morphotype. In a large RCT LIVE study [32] that assigned patients to a “standard” lung protective mechanical ventilation protocol or to a personalized approach based on a focal or nonfocal morphology of consolidations on computed tomography (CT)-imaging of the lung a personalized ventilatory strategy does not consider mortality versus a standard care strategy. However, this study proves that a misaligned mechanical ventilator strategy increases mortality. These results tend to establish the significance to adapt the good strategy for each morphotype of ARDS.

Nevertheless, determining the morphology of lung injuries during ARDS is challenging. In the LIVE study, the investigators misclassified the lung morphology of 21% of the 400 patients. Analysis of patients for whom their lung morphology was correctly classified and misclassified differed, which resulted in incorrect conclusions [32]. This example shows the difficulty associated with correctly classifying lung morphology because no specific definition or diagnostic tools exist for the accurate identification of lung morphology for lung injuries contributing to ARDS. Developing alternative (imaging) modalities that can accurately identify focal and nonfocal ARDS morphology should constitute the future research agenda of precision medicine, as this topic deserves investigations [45].

There are also limitations in this study and controversies of using volatile agents within the ICU. First, volatile agents are well known triggers for patients genetically predisposed to malignant hyperthermia. A case of malignant hyperthermia has been identified during sevoflurane therapy in a patient with pneumonia [46]. However, this condition remains rare (1/50,000–100,000) in comparison to propofol infusion syndrome, which affects up to 1% of ICU patients [47]. Second, some types of patients may be unsuitable for inhalation sedation secondary to equipment limitations. The ideal weight-based tidal volume with the AnaConDa® is unknown but a minimum tidal volume of 350 mL for pediatric patients is recommended to overcome device dead space and avoid rebreathing of carbon dioxide. This may not be feasible in smaller patients who require lung-protective (6 mL/kg predicted body weight (PBW)) or even ultra-protective (<4 mL/kg PBW) ventilation protocols and those who need one-lung ventilation strategies. This device may also become impractical in patients with high-volume bronchial secretions, which may occlude and prevent optimal drug delivery. Hopefully, a miniaturized version of the AnaConDa® (AnaConDa-S®, Sedana Medical, Uppsala, Sweden) has been recently developed thus decreasing the device dead space to approximately 50 mL and allowing a minimum tidal volume of 200 mL. Of note, our recent experience of inhaled sevoflurane using the AnaConDa® in

ICU patients with ARDS supports its feasibility and safety in particular with regards to its respiratory and hemodynamic effects [11]. Third, fluoride ions are constituents of all volatile agents and they were not measured in this study. Historical work during the 1970s identified that fluoride levels beyond 50  $\mu\text{mol/L}$  can impair the renal tubular concentrating ability leading to high-output renal failure [48]. This safety threshold has continued to be used despite modern-day anesthetic drugs displaying markedly different pharmacokinetic profiles. The elimination half-life of serum fluoride ions is 21.4 to 24.8 hours. Sevoflurane has 7 fluoride ions but undergo low levels of metabolism to produce inorganic fluoride. Serum fluoride levels do rise during both short anesthetic and longer ICU duration of use, with sevoflurane displaying higher levels than isoflurane given its greater metabolism and fluoride content [49,50]. However, no significant association between renal dysfunction and fluoride levels has been identified despite several patients displaying levels beyond 50  $\mu\text{mol/L}$  [50]. Taken together, no significant effect of inhaled sevoflurane on renal function has been observed to date in clinical studies of ICU patients. Fourth, other elements could influence the pharmacokinetics of sevoflurane such as the overall ventilation/perfusion ratio genetic polymorphisms [51]. Such elements have not been studied in the SPIDERMAN study and we could not exclude that they could impact the results [45]. Finally, pharmacokinetics are demanding studies in terms of sample collection and dose modifications. In intensive care, patients are unstable with very rapid progression, which further complicates this type of study particularly in this environment.

## **CONCLUSION**

In conclusion, the SPIDERMAN study is the first study that was primarily designed to assess the pharmacokinetics of sevoflurane according to the difference of the morphology of the lung injury during ARDS (i.e., between focal and nonfocal) in ICU patients. In this interim analysis, sevoflurane used for inhaled sedation did not present distinct pharmacokinetic profiles depending on lung imaging phenotypes (focal versus nonfocal) during ARDS in ICU patients. This study improves the understanding of halogenated agents used in the sedation in ICU of ARDS patients. The SPIDERMAN study falls within the aim of personalized medicine that is to identify, select, and test therapies that are most likely to be associated with a favorable outcome in a specific patient.

## **DECLARATIONS**

### *Ethics approval and consent to participate*

The SPIDERMAN study will be conducted in accordance with the Declaration of Helsinki and has been registered at <http://www.clinicaltrial.gov> on July 17, 2019 with identification number NCT04023305. The study protocol was approved by the ethics committee *CPP Ile de France VIII* and the ANSM in May 2019 (approval number N°EudraCT\_2018\_003511\_21).

### *Consent for publication*

Not applicable

### *Availability of data and materials*

Not applicable

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# CONCLUSION DE THÈSE

## CONCLUSION DU TRAVAIL DE THÈSE

### **Étude du profil pharmacocinétique et pharmacodynamique du sévoflurane en fonction de la morphologie de l'atteinte pulmonaire au cours de l'utilisation de la sédation inhalée chez les patients de réanimation en syndrome de détresse respiratoire aiguë**

(Impact of lung imaging phenotypes on sevoflurane pharmacokinetics and pharmacodynamics during inhaled sedation in patients with acute respiratory distress syndrome: SPIDERMAN A case-control study.)

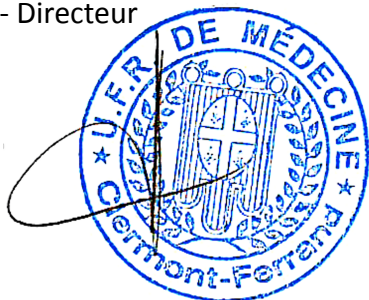
L'étude SPIDERMAN est la première étude clinique s'intéressant au profil pharmacocinétique et pharmacodynamique du sévoflurane en fonction de la morphologie de l'atteinte pulmonaire au cours du syndrome de détresse respiratoire aiguë (SDRA) chez des patients admis en réanimation.

L'atteinte pulmonaire au cours du SDRA est caractérisée par des anomalies d'aération au niveau du parenchyme pulmonaire associées à des anomalies de perfusion. Il est donc primordial de mieux comprendre et caractériser l'impact de la morphologie de l'atteinte pulmonaire sur la pharmacologie, les effets protecteurs pulmonaires et les effets sédatifs des agents halogénés afin de pouvoir les utiliser de manière usuelle chez des patients présentant un SDRA et nécessitant de la ventilation mécanique.

L'analyse intermédiaire à 10 x 2 patients ne retrouve pas de relation statistiquement significative entre le morphotype, focal et non focal, du SDRA et la pharmacocinétique du sévoflurane pendant la sédation inhalée du patient atteint de SDRA en réanimation.

Cette étude s'inscrit dans une dynamique d'approche personnalisée des stratégies thérapeutiques au cours du SDRA.

Clermont-Ferrand, le 23/09/2022  
Pierre CLAVELOU  
Doyen - Directeur



Clermont-Ferrand, le 21/09/2022  
Le Président du Jury Pr FUTIER Emmanuel

# ANNEXES

## APPENDIX I: SpO<sub>2</sub>/ FiO<sub>2</sub> ratio inclusion criteria

The table below displays an equivalence table that determines the estimated P/F ratio from the FiO<sub>2</sub> and SpO<sub>2</sub>. This data was generated by investigators at the University of Utah, on a cohort of critically ill patients with pneumonia.

Imputed PaO<sub>2</sub>/ FiO<sub>2</sub> for combination of SpO<sub>2</sub> (rows) and FiO<sub>2</sub> (columns)

SPO2	FiO2														
	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

For altitude adjustment, we would recommend the practice from ARDS Network studies of multiplying the qualification threshold PaO<sub>2</sub>/FiO<sub>2</sub> by the ratio of average ambient to sea level barometric pressure (for Utah, it is 0.86\*150 = 129; for Denver it is 0.84\*150 = 126).

Additional requirements for the use of the SaO<sub>2</sub>/FiO<sub>2</sub> ratio include:

1. SpO<sub>2</sub> between 80-96%
2. SpO<sub>2</sub> should be measured at least 10 minutes after any change in FiO<sub>2</sub>.
3. PEEP ≥ 8cmH<sub>2</sub>O .
4. An adequate pulse oximeter waveform tracing.

## APPENDIX II: Time-Events Schedule

Measurement/Event	Day 0	1	2	3	4	5	6	7
Demographics, History and Physical	X							
Etiology of ARDS	X							
APACHE II, SAPS II	X							
HCG (females)	X							
Alcohol Use/Smoking History	X							
Assessment of lung morphology	X							
Sevoflurane pharmacokinetics (plasma concentration at time T1 to T7) <sup>1</sup>	X	X	X					
HFIP pharmacokinetics (plasma concentration at time T1 to T7) <sup>1</sup>	X	X	X					
Sevoflurane pharmacokinetics (plasma concentration at time T8 to T13) <sup>2</sup>				(X)	(X)	(X)	(X)	(X)
HFIP pharmacokinetics (plasma concentration at time T8 to T13) <sup>2</sup>				(X)	(X)	(X)	(X)	(X)
Infusion rate of sevoflurane	X	X	X	(X)	(X)	(X)	(X)	(X)
F <sub>E</sub> sevo, F <sub>I</sub> sevo and EtCO <sub>2</sub>	X	X	X	(X)	(X)	(X)	(X)	(X)
Infusion rate of remifentanyl	X	X	X	(X)	(X)	(X)	(X)	(X)
BIS values	X	X	X	(X)	(X)	(X)	(X)	(X)
Infusion rate of cisatracurium	X	X	X	(X)	(X)	(X)	(X)	(X)
Ventilator parameters	X	X	X	(X)	(X)	(X)	(X)	(X)
Use of rescue procedures	X	X	X	(X)	(X)	(X)	(X)	(X)
On-study meds: sedative, opioid, corticosteroid administration	X	X	X	(X)	(X)	(X)	(X)	(X)
Sedation score if RASS<-1	X	X	X	(X)	(X)	(X)	(X)	(X)
Sedation interruption performed	X	X	X	(X)	(X)	(X)	(X)	(X)
SOFA Score (modified)	X	X	X	(X)	(X)	(X)	(X)	(X)
Serum liver function tests (AST, ALT, bilirubin, INR)	X	X	X	(X)	(X)	(X)	(X)	(X)
Fluid (intake/output)/ Central Venous Pressure	X	X	X	(X)	(X)	(X)	(X)	(X)
Hemodynamic parameters	X	X	X	(X)	(X)	(X)	(X)	(X)
KDIGO criteria for acute kidney injury	X	X	X	(X)	(X)	(X)	(X)	(X)
Arterial Blood Gases	X	X	X	(X)	(X)	(X)	(X)	(X)

<sup>1</sup> Measure the plasma concentration of sevoflurane 5 min, 30 min, 1h, 6h, 12h, 24h, and 48h after the detection of sevoflurane (0,1%) by the monitor in the breathing. (T1=5 min; T2=30 min; T3=1h; T4=6h; T5=12h; T6=24h; T7=48h.)

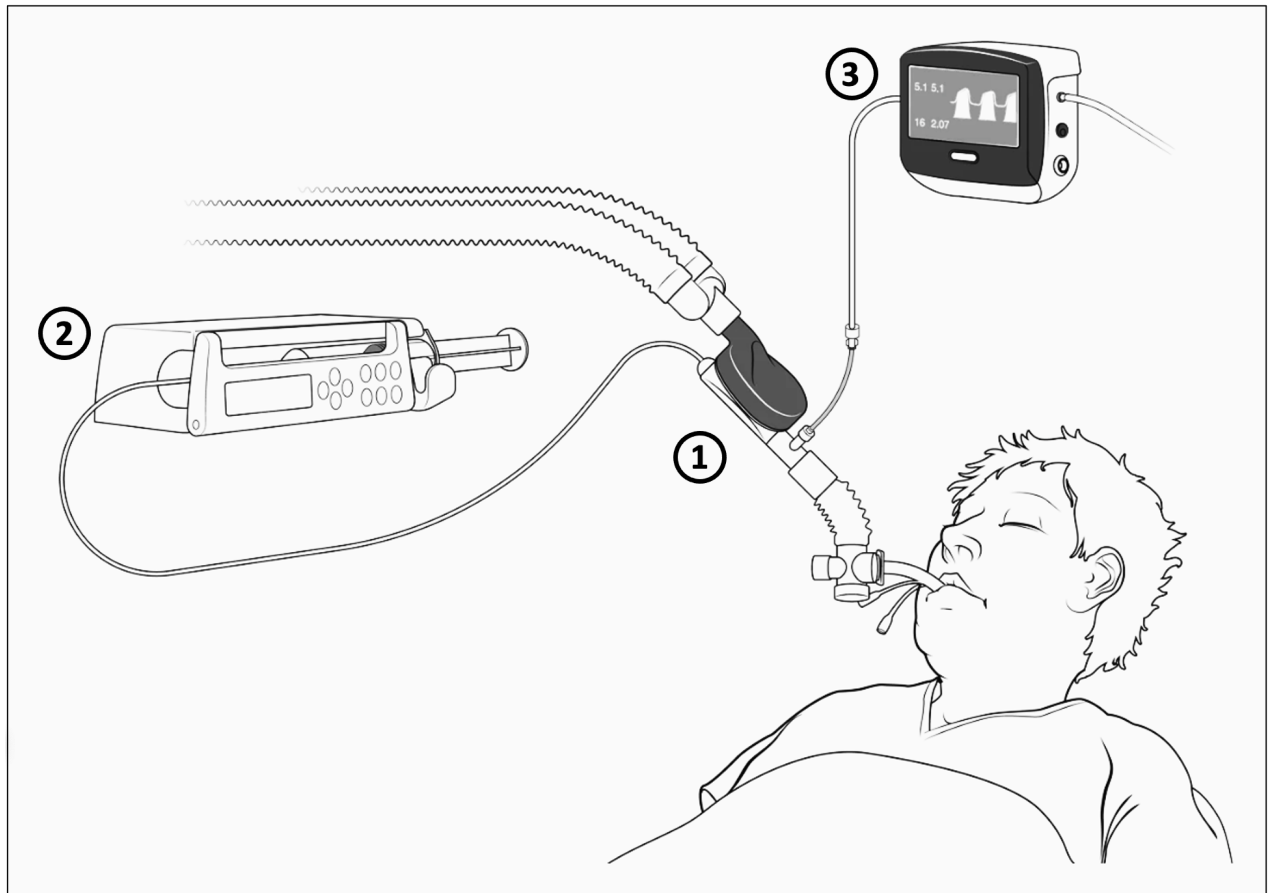
<sup>2</sup> Measure the plasma concentration of sevoflurane immediately 5 min, 30 min, 1h, 4h, and 6h after cessation of sevoflurane administration (T8=stop inhaled sevoflurane; T9=+5 min after stop; T10=+30 min after stop; T11=+1h after stop; T12=+ 4h after stop; T13=+6h after stop)

X = Required

(X) = Required but time will depend to the day of stop of sevoflurane

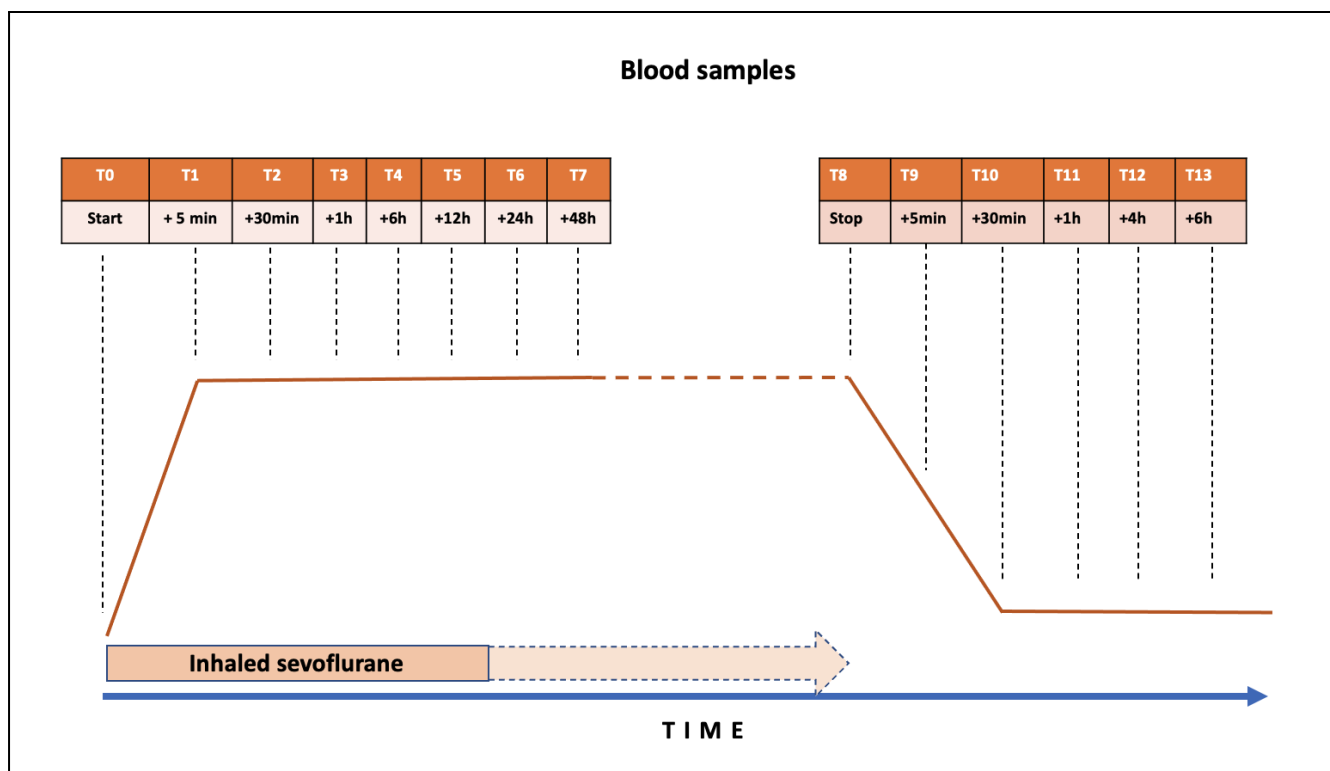
## APPENDIX III: AnaConDa device

<https://sedanamedical.com/products/anaconda>



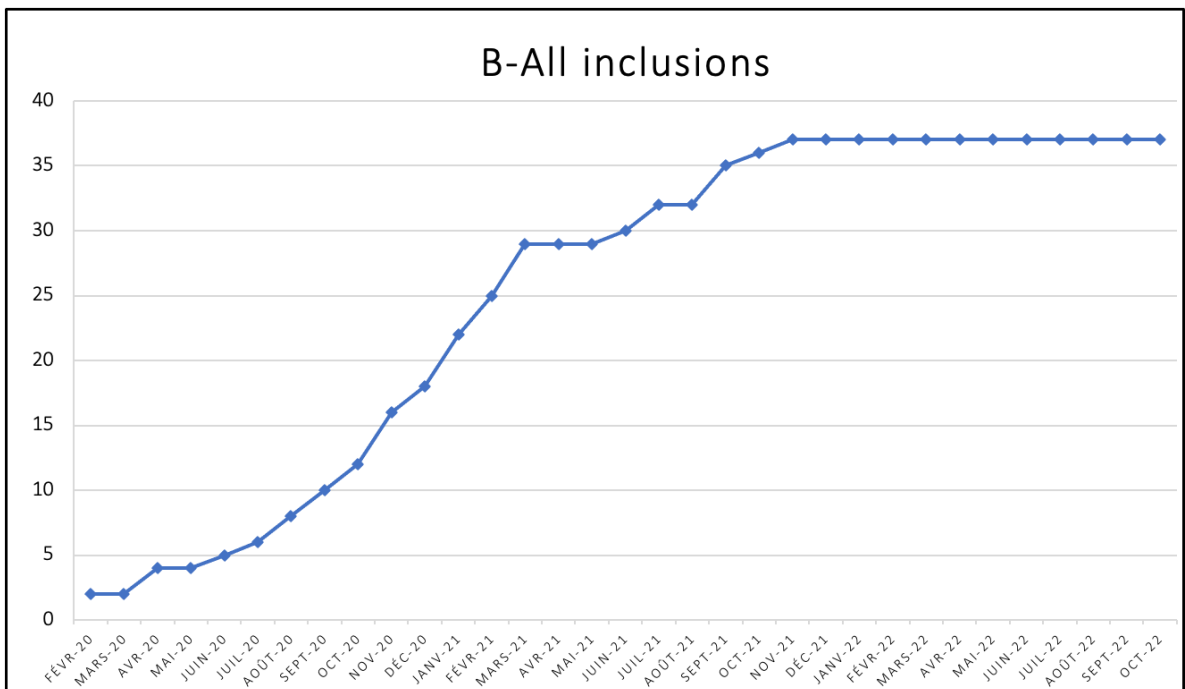
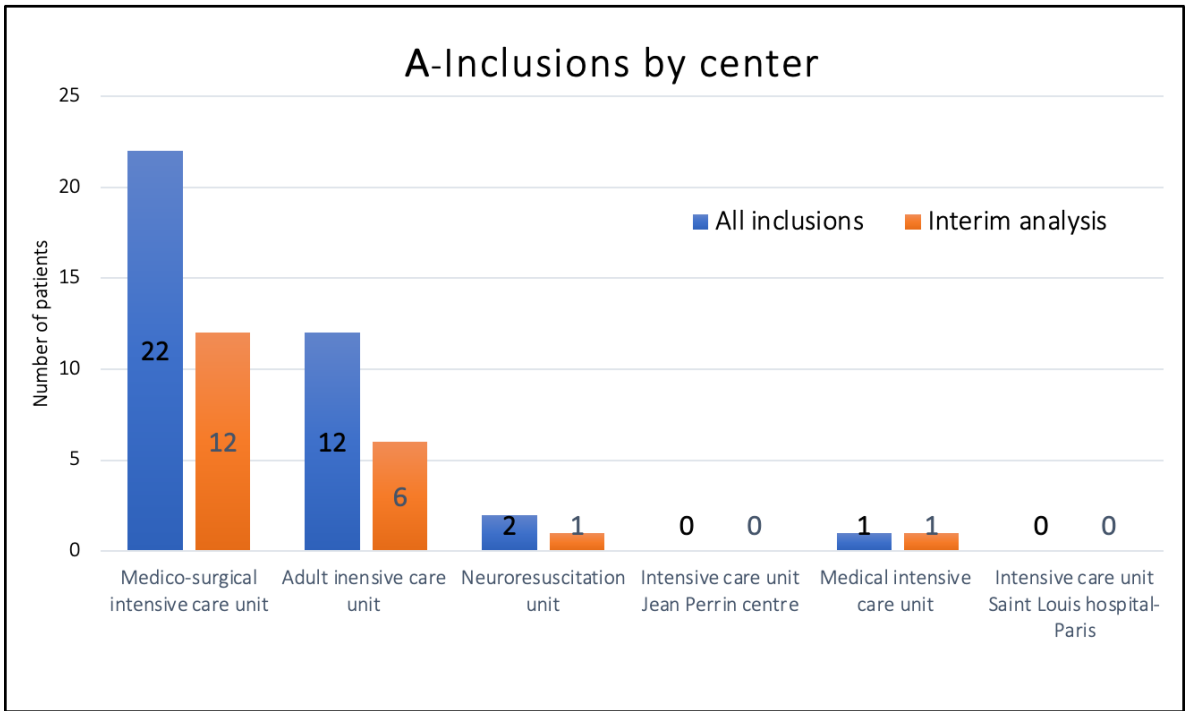
1. ANACONDA-S
2. Sevofluran syringe driver
3. Gas analyzer (inspired and expired fraction of sevoflurane, ETCO<sub>2</sub>)

## APPENDIX IV: Timeline of blood samples collection



## APPENDIX V: Distribution of inclusions

Inclusions by center Figure-A and the rhythm of inclusions Figure-B.





**APPENDIX VI:** Evolution of sevoflurane and hexafluoroisopropanol plasma concentration (mg/l).

Results are expressed as means  $\pm$  SD. P-value of time group (nonfocal versus focal) interaction.

Parameters	Nonfocal (N=10) Mean $\pm$ SD	Focal (N=10) Mean $\pm$ SD	Time x group interaction P-value
<b>Sevoflurane plasma concentration (mg/l)</b>			
<b>T0 (Start sevoflurane)</b>	0	0	--
T1 (5 min)	15.85 $\pm$ 12.53	26 $\pm$ 20.2	0.35
T2 (30 min)	27.73 $\pm$ 12.74	36.95 $\pm$ 22.46	0.37
T3 (1h)	31.76 $\pm$ 11.63	39.5 $\pm$ 23.31	0.48
T4 (6h)	47.64 $\pm$ 23.16	45.43 $\pm$ 24.9	0.84
T5 (12h)	44.25 $\pm$ 25.65	44.82 $\pm$ 25.28	0.95
T6 (24h)	50.31 $\pm$ 23.53	44.1 $\pm$ 27.93	0.48
T7 (48h)	64.47 $\pm$ 61.12	63.1 $\pm$ 31.15	0.68
<b>T8 (0 min, stop Sevoflurane)</b>	54.33 $\pm$ 28.5	35.12 $\pm$ 21.31	0.07
T9 (5 min)	44.32 $\pm$ 22.81	27.48 $\pm$ 15.48	0.12
T10 (30 min)	34.16 $\pm$ 23.66	24 $\pm$ 16.26	0.35
T11 (1h)	30.83 $\pm$ 17.72	20 $\pm$ 10.93	0.32
T12 (4h)	15.73 $\pm$ 8.71	23.9 $\pm$ 24.6	0.45
T13 (6h)	18 $\pm$ 9.24	19.74 $\pm$ 21	0.87
<b>Hexafluoroisopropanol plasma concentration (mg/l)</b>			
<b>T0 (Start sevoflurane)</b>	0	0	--
T1 (5 min)	0.38 $\pm$ 0.45	1 $\pm$ 1.8	0.25
T2 (30 min)	0.55 $\pm$ 0.42	0.74 $\pm$ 0.6	0.16
T3 (1h)	0.64 $\pm$ 0.48	1.94 $\pm$ 2.8	0.01
T4 (6h)	0.93 $\pm$ 0.54	1.63 $\pm$ 2.3	0.19
T5 (12h)	0.98 $\pm$ 0.45	1.85 $\pm$ 2.7	0.10
T6 (24h)	1 $\pm$ 0.25	1.1 $\pm$ 0.12	0.42
T7 (48h)	1.35 $\pm$ 1	2.6 $\pm$ 2.96	0.18
<b>T8 (0 min, stop Sevoflurane)</b>	1.22 $\pm$ 0.62	2 $\pm$ 2.67	0.10
T9 (5 min)	1.14 $\pm$ 0.75	2.2 $\pm$ 3.46	0.04
T10 (30 min)	1.37 $\pm$ 0.78	1.9 $\pm$ 2	0.33
T11 (1h)	1.27 $\pm$ 0.7	1.74 $\pm$ 1.5	0.38
T12 (4h)	1.18 $\pm$ 0.68	1.81 $\pm$ 1.82	0.24
T13 (6h)	1.41 $\pm$ 0.93	1.64 $\pm$ 1.73	0.67

## APPENDIX VII: Sevoflurane administration features:

Infusion rate, end-expiratory fraction and end-inspiratory fraction in nonfocal and focal ARDS groups. Results are expressed as means  $\pm$  SD. P-value of time group (nonfocal versus focal) interaction.

Parameters	Nonfocal (N=10) Mean $\pm$ SD	Focal (N=10) Mean $\pm$ SD	Time x group interaction P-value
<b>Sevoflurane infusion rate (ml/h)</b>			
<b>T0 (Start sevoflurane)</b>	4.35 $\pm$ 3.5	3.7 $\pm$ 3.7	–
T1 (5 min)	6.2 $\pm$ 2	5.9 $\pm$ 1.6	0.86
T2 (30 min)	8.9 $\pm$ 4.3	7.4 $\pm$ 1.7	0.56
T3 (1h)	9.9 $\pm$ 5.8	7.9 $\pm$ 1.7	0.33
T4 (6h)	8.3 $\pm$ 8.2	8.2 $\pm$ 2.5	0.89
T5 (12h)	9.25 $\pm$ 3.6	7.6 $\pm$ 1.8	0.48
T6 (24h)	8.72 $\pm$ 2.3	8.7 $\pm$ 3	0.70
T7 (48h)	9.37 $\pm$ 2.6	10 $\pm$ 5.1	0.38
<b>T8 (0 min, stop Sevoflurane)</b>	5.2 $\pm$ 4.6	1.45 $\pm$ 2.2	0.03
T9 (5 min)	0	0	0.65
T10 (30 min)	0	0	0.65
T11 (1h)	0	0	0.65
T12 (4h)	0	0	0.65
T13 (6h)	0	0	0.65
<b>Sevoflurane end-inspiratory fraction (%)</b>			
<b>T0 (Start sevoflurane)</b>	0.09 $\pm$ 0.28	0.01 $\pm$ 0.03	–
T1 (5 min)	0.3 $\pm$ 0.23	0.27 $\pm$ 0.12	0.60
T2 (30 min)	0.43 $\pm$ 0.11	0.47 $\pm$ 0.12	0.19
T3 (1h)	0.51 $\pm$ 0.15	0.54 $\pm$ 0.1	0.25
T4 (6h)	0.53 $\pm$ 0.17	0.49 $\pm$ 0.16	0.74
T5 (12h)	0.53 $\pm$ 0.22	0.49 $\pm$ 0.16	0.69
T6 (24h)	0.53 $\pm$ 0.18	0.59 $\pm$ 0.17	0.23
T7 (48h)	0.56 $\pm$ 0.26	0.58 $\pm$ 0.25	0.39
<b>T8 (0 min, stop Sevoflurane)</b>	0.54 $\pm$ 0.26	0.35 $\pm$ 0.22	0.27
T9 (5 min)	0.24 $\pm$ 0.16	0.27 $\pm$ 0.32	0.28
T10 (30 min)	0.1 $\pm$ 0.14	0.085 $\pm$ 0.12	0.61
T11 (1h)	0.06 $\pm$ 0.1	0.03 $\pm$ 0.01	0.68
T12 (4h)	0.02 $\pm$ 0.06	0.01 $\pm$ 0.03	0.51
T13 (6h)	0.03 $\pm$ 0.1	0 $\pm$ 0	0.66
<b>Sevoflurane end-expiratory fraction (%)</b>			
<b>T0 (Start sevoflurane)</b>	0.16 $\pm$ 0.47	0.01 $\pm$ 0.03	–
T1 (5 min)	0.51 $\pm$ 0.28	0.56 $\pm$ 0.26	0.28
T2 (30 min)	0.65 $\pm$ 0.15	0.78 $\pm$ 0.15	0.12
T3 (1h)	0.78 $\pm$ 0.09	0.89 $\pm$ 0.11	0.17
T4 (6h)	0.96 $\pm$ 0.26	0.9 $\pm$ 0.3	0.63
T5 (12h)	1.05 $\pm$ 0.42	1 $\pm$ 0.11	0.56
T6 (24h)	1.05 $\pm$ 0.26	1 $\pm$ 0.22	0.43
T7 (48h)	0.98 $\pm$ 0.26	1.2 $\pm$ 0.53	0.08
<b>T8 (0 min, stop Sevoflurane)</b>	1.39 $\pm$ 1	0.76 $\pm$ 0.31	0.01
T9 (5 min)	0.72 $\pm$ 0.45	0.51 $\pm$ 0.21	0.77
T10 (30 min)	0.4 $\pm$ 0.15	0.29 $\pm$ 0.19	0.83
T11 (1h)	0.28 $\pm$ 0.19	0.25 $\pm$ 0.13	0.56
T12 (4h)	0.12 $\pm$ 0.14	0.14 $\pm$ 0.11	0.41
T13 (6h)	0.075 $\pm$ 0.14	0.1 $\pm$ 0.1	0.37

## APPENDIX VIII: The evolution of the PaO<sub>2</sub>/FiO<sub>2</sub> ratios.

Results are expressed as means ± SD. P-value of time group (nonfocal versus focal) interaction.

Parameters	Nonfocal (N=10) Mean ± SD	Focal (N=10) Mean ± SD	Time x group interaction <i>P-value</i>
<b>PaO<sub>2</sub>/FiO<sub>2</sub> ratios</b>			
<b>T0 (Start sevoflurane)</b>	108 ± 36.6	134 ± 54	--
T1 (5 min)	111 ± 49.2	138 ± 52	0.96
T2 (30 min)	126 ± 62.19	140 ± 42	0.55
T3 (1h)	125 ± 56.5	133 ± 34	0.35
T4 (6h)	142 ± 35.1	158 ± 51	0.66
T5 (12h)	139 ± 38.3	181 ± 56.44	0.58
T6 (24h)	149 ± 31.3	178 ± 59.5	0.81
T7 (48h)	133 ± 42.1	168.8 ± 37.1	0.38
<b>T8 (0 min, stop Sevoflurane)</b>	139 ± 34.88	221 ± 82.9	0.02
T9 (5 min)	137 ± 36.6	209 ± 61.52	0.07
T10 (30 min)	132 ± 37.6	211 ± 65.3	0.06
T11 (1h)	135 ± 32.7	203 ± 63.22	0.15
T12 (4h)	131 ± 30	209 ± 62.33	0.04
T13 (6h)	141 ± 22	198 ± 53	0.24

## SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

## **SERMENT D'HIPPOCRATE VERSION COURTE**

En présence des Maîtres de cette Faculté et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis à l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

## ABSTRACT

**Background:** Lung morphology (focal and nonfocal) of injury during acute respiratory distress syndrome (ARDS) has a major impact on outcomes and reflects the severity of lung injury. Sevoflurane is safe and associated with improved oxygenation, reduced levels of some pro-inflammatory markers and reduced lung epithelial injury. Data suggest differential responses to sevoflurane in focal and nonfocal ARDS phenotypes, but the mechanism remains unknown. The aim of this study is to compare the pharmacokinetic of sevoflurane-induced sedation during ARDS depending on the lung morphology.

**Methods:** The SPIDERMAN study is a case control study in six ICU. Two groups of patients with moderate-to-severe ARDS will be enrolled, depending on their lung morphotype (focal or nonfocal). These patients will receive inhaled sevoflurane as a standard practice of sedation. The primary endpoint is the determination of plasma concentrations of sevoflurane in patients with focal and those with nonfocal ARDS. Plasma concentrations of sevoflurane will be measured in both study groups from the start of sedation up to 48h at specific time-points and immediately after cessation of sevoflurane up to 6h. The secondary endpoints include the report of plasma concentration of hexafluoroisopropanol, the fraction of inspired and expired sevoflurane, the infusion rates of sevoflurane, the infusion rates of remifentanyl, the bispectral index values, the evolution of renal function and  $\text{PaO}_2 / \text{FIO}_2$  ratios between patients with focal and nonfocal ARDS. 40 patients will be recruited.

**Results:** A total of 20 patients have been included in the study for the interim analysis. The plasma concentrations of sevoflurane and HFIP were not different between two groups. No significant differences were observed between the focal and nonfocal ARDS groups for the sevoflurane administration features, bispectral index,  $\text{PaO}_2 / \text{FIO}_2$ . no impact on renal function.

**Conclusion:** In interim analysis no significant difference in the pharmacokinetics of sevoflurane in the nonfocal compared to focal ARDS patients.

**Keywords:** ARDS, sevoflurane, inhaled sedation, halogenated agent, morphotype, focal, nonfocal, ICU.

