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**Minimal alveolar concentration for deep sedation (MAC-DS) in intensive care unit patients sedated
with sevoflurane: a physiological study**

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Minimal alveolar concentration for deep sedation (MAC-DS) in intensive care unit patients sedated with sevoflurane: a physiological study

INTRODUCTION

Over the last 20 years, the concept of sedation in intensive care unit (ICU) has shifted from deep and prolonged sedation to a light and short one. Nowadays, deep sedation should be avoided except in some selected patients: severe trauma brain injury, acute respiratory distress syndrome (ARDS), important haemodynamic instability [1]. Targeting light sedation supports the use of protocolised sedation algorithm that allowed to reduce both mechanical ventilation duration and ICU length of stay [2,3]. These protocols are based on the evaluation of the level of vigilance using a clinical (or sedation) scale such as Ramsay scale or Richmond Assessment Sedation Score [4,5].

Different drugs are available to achieve such sedative strategies. The parenteral route is classically used with current guidelines focusing only on intravenous sedative agents [6]. However, volatile anaesthetic agents represent another option, especially when deep sedation is required. Indeed, volatile anaesthetic agents have favourable pharmacokinetics: pulmonary elimination, limited hepatic and renal metabolism, no accumulation, quick and consistent onset and offset of action [1,7]. Several trials support the efficacy and safety of volatile anaesthetic agents for the sedation in ICU patients [8,9]. Compared with intravenous agent, Sevoflurane was associated with shorter wake-up and extubation times [10]. Sevoflurane may also improve gas exchange and inflammation in ARDS [11].

In the operating theatre, volatile anaesthetic agents are monitored using minimal alveolar concentration (MAC) [12]. MAC is defined as “the end-tidal concentration of inhaled anaesthetic that ablates movement in response to surgical incision in 50 percent of a test population” [12,13]. Among variables able to influence MAC, age is a major one, with a decrease of about 6% of MAC per decade [14]. Starting from MAC, several other parameters have been created (MAC-awake, MAC-immobility...) and are used to describe the end-tidal concentration that ablates a certain stimulation [12].

During sedation in ICU with volatile anaesthetic agents, MAC may be used to assess sedation level and may replace clinical scale, especially when they are unusable. Indeed, most of sedation scales require a motor assessment. However, patient requiring deep sedation also usually require neuromuscular blockade and therefore prohibits the use of these scales [15,16]. Hence, MAC may be of particular value for assessing sedation level. We therefore conducted a study in which we sought to investigate the minimal sevoflurane end-tidal concentration to achieved deep sedation in ICU patients leading to describe a MAC derivatives that we called MAC-deep sedation (MAC-DS).

MATERIALS AND METHODS

Design and Patients: It was a prospective interventional study in the ICU of Clermont-Ferrand hospital, a French tertiary hospital [17]. Consecutive patients hospitalised in ICU were included if they were older than 18, requiring ventilation for at least 6 hours and had a Richmond Assessment Sedation Score (RASS) of 0 without any sedation. Patients were not included if they had any haemodynamic instability, sevoflurane anaphylaxis and known or suspected risk for malignant hyperthermia. Furthermore, pregnant or lactating women were not included.

Ethics: According to the current French law, the study was approved by the “Institutional Review Board of Clermont-Ferrand, France” (N°EudraCT 2014-000759-10) and registered on *clinicaltrials.gov* (NCT 02202720) [18]. Before any inclusion, written informed consent was obtained from patient or their relatives.

Outcomes: The main outcome of this study was to establish the MAC of sevoflurane needed to get a deep sedation (MAC-DS), assessed by the RASS [19]. Deep sedation was defined by a RASS \leq -3 (i.e. RASS = -3, -4 or -5). To be clinically relevant, we chose to define MAC-DS as the minimal sevoflurane end-tidal concentration to get 90% and 95% of patients in deep sedation (MAC-DS₉₀ and MAC-DS₉₅, respectively). MAC-DS value was calculated and reported as a Sevoflurane expiratory fraction value (FeSevo) or a fraction of the classic age-adjusted MAC. Another outcome of this study was to determine if a processed electroencephalographic activity, assessed by the Bispectral index (BIS, Aspect Medical Systems, Norwood, MA, USA), was an efficient surrogate of sedation levels in ICU patients treated with sevoflurane.

Intervention: Demographic and biological data were recorded before any intervention. No patient received sevoflurane before inclusion. Sevoflurane was administered using the Mirus™ system (Pall Medical, Dreieich, Germany) allowing sevoflurane deliverance with an automatic feedback of the desired age-adjusted MAC. Each patient was managed by a single investigator usually trained to assess sedation level in ICU. Sevoflurane was started after inclusion, and the

targeted age-adjusted MAC of Sevoflurane was stepwise increased by 0.1 MAC each 30 minutes from MAC 0 to MAC 0.8, based on preliminary evaluation. After reaching MAC 0.8, sevoflurane concentrations were decreased using the same steps (Figure 1). At each step, an infusion of remifentanyl was adjusted to get an optimal analgesia based on Behavioural Pain Scale (BPS) ≤ 4 [20]. Fifteen minutes after each sevoflurane MAC stepwise, FeSevo, haemodynamic parameters (systolic, diastolic and mean arterial blood pressure, heart rate, norepinephrine doses), respiratory parameters (end tidal CO₂, respiratory rate, inspired fraction of oxygen, positive end expiratory pressure, ventilator mode), BIS and BPS were recorded before RASS evaluation to avoid any bias due to patient stimulation mandatory for RASS estimation.

Statistical analysis: A descriptive analysis was performed in all patients. Quantitative variables are expressed as median [interquartile range (IQR), 25-75%]. Categorical variables are expressed as numbers (%). A Spearman's rank correlation coefficient was used to assess the correlation between numerical variables. Data were subjected to logistic regression analysis to estimate the MAC-DS₉₀ and MAC-DS₉₅. Data analysis was performed using random effects models that allow intra- and inter-subject variability to be considered. Receiver operating characteristics (ROC) curves analysis was performed to assess the ability of BIS to predict deep sedation. The optimal cut-off value was chosen to maximise sensitivity and specificity using the Youden index. A *P* value of ≤ 0.05 was considered to be statistically significant. Statistical analyses were carried out using R version 3.6.2 for MacOS® (<https://www.r-project.org>, accessed February 2020).

RESULTS

Population: Between June and November 2014, 30 patients were included (median (IQR) age 60 (47-69) years, 19 male). Their main characteristics are reported in Table 1. Briefly, at inclusion, the RASS was of 0 for all patients and the median BIS was 93 [79-97]. Nineteen and 11 patients were admitted to ICU for postoperative cares and medical diseases with difficult weaning from mechanical ventilation, respectively. During all the intervention, neither BPS ($p = 1$) or remifentanil infusion ($p = 0.180$) changed.

Minimal alveolar concentration of Sevoflurane needed to get a deep sedation (MAC-DS): Increasing Sevoflurane MAC was strongly correlated with a decrease in RASS values ($r = -0.83$, $p < 0.001$). MAC-DS₉₀ and MAC-DS₉₅ were achieved at 0.42 age-adjusted MAC (95% confidence interval (IC95) [0.38-0.46]) and 0.46 age-adjusted MAC (IC95 [0.42-0.51]), respectively. RASS levels for each FeSevo are reported in Figure 2. Likewise, increasing FeSevo was associated with a decrease in RASS values ($r = -0.79$, $p < 0.001$). FeSevo to achieve MAC-DS₉₀ and MAC-DS₉₅ was 0.72% (IC95 [0.65-0.79]) and 0.80% (IC95 [0.72-0.89]), respectively.

Bispectral index and sedation level: Increasing sevoflurane MAC or FeSevo was correlated with a decrease in BIS values ($r = -0.64$, $p < 0.001$ and $r = -0.64$, $p < 0.001$ respectively). Likewise, there was a moderate correlation between RASS levels and BIS values ($r = 0.63$, $p < 0.001$). ROC curve analysis revealed an area under the curve for BIS of 0.88 (IC95 [0.85-0.91]) (Figure 3A). The optimal threshold was obtained at 72 leading to a sensitivity of 0.79 (IC95 [0.75-0.84]) and specificity of 0.81 (IC95 [0.76-0.87]). However, during deep sedation, the spread of BIS value was ranging from 24 up to 98 (Figure 3B). Indeed, while in deep sedation, 67 measures (21%) were over 72 of BIS (red square in Figure 3B). On the other hand, there were 34 measures (18%) of BIS beneath 72 with RASS over -3 (blue square in Figure 3B).

DISCUSSION

This was the first study describing the monitoring of sedation level in ICU by the correlation between RASS (and deep sedation when $RASS \leq -3$) and MAC (called MAC-DS). In 30 ICU patients, MAC-DS₉₀ was achieved with 0.4 age-adjusted MAC of sevoflurane or a FeSevo of 0.7%. MAC-DS₉₅ was achieved with 0.5 age-adjusted MAC of sevoflurane or a FeSevo of 0.8%. These findings mean that Monitoring FeSevo could replace RASS monitoring when RASS is unavailable, such as in ARDS patients with neuromuscular blockade.

MAC was the first quantitative method to assess anaesthetic potency and still remains a standard index for comparison of different volatile anaesthetic [14]. By definition, MAC represents the effective concentration to prevent any movement in 50% of patients after a surgical incision [13]. In our study, MAC-DS was defined as the minimal sevoflurane end-tidal concentration to get patients in deep sedation. However, in order to be clinically pertinent, we chose to focus our investigation on MAC-DS₉₀ and MAC-DS₉₅: MAC-DS to get 90% and 95% patients in deep sedation, respectively. This choice was justified by current indications of deep sedation, usually requiring neuromuscular blockade, which does not allow any inadequate sedation [1].

Our definition of MAC-DS allowed different surrogate of end-tidal concentration. We chose to present our result with two different parameters: a fraction of the classic age-adjusted MAC or the expired fraction of sevoflurane (FeSevo). In ICU, two different technical devices are actually used as anaesthetic reflector for vaporising volatile anaesthetic agents [21]: The Mirus device (Pall Medical, Dreieich, Germany), which has its own monitor for gas concentration allowing to deliver sevoflurane with an automatic feedback of the desired MAC, reporting both FeSevo and MAC [22], and the AnaConDa device (SEDANA Medical, Uppsala, Sweden), which requires an external gas monitor to report early inspiratory peak concentrations, considered as an end-tidal concentration [23,24]. Yet, only FeSevo is reported, which requires a MAC calculation by the physician. In our study, we report MAC-DS as a FeSevo value. However, we also decide to present our result as a fraction of the classic

MAC in order to avoid a potential bias due to the spread of age in our cohort. Indeed, patient age is the main factor affecting MAC. Yet, our FeSevo findings may significantly change with patient age. That matter can be avoided using a fraction of the classic age-adjusted MAC as a surrogate of MAC-*DS*.

Previous study focusing on volatile anaesthetic agents in ICU had similar result on end-tidal concentration needed to get a sedative effect. In two studies comparing time to extubation and length of stay between sevoflurane and propofol infusion in postoperative patients requiring intensive cares, Rhom et al. reported an end-tidal concentration of 0.5-1% to get a RASS between -3 and -4 [25,26]. Furthermore, in patients with ARDS, Jabaudon et al. needed an expired fraction of sevoflurane of 0.6-0.7% to get a deep sedation defined by a RASS = -5 [11]. Finally, an adjusted-age 0.1-0.3 MAC of sevoflurane allowed a light sedation with patients between RASS -1 and 1 [27]. Increasing this MAC to 0.5 was similar to an infusion of at least 2mg/kg/h of propofol [28].

Beside MAC-*DS*, our study reports the use of processed electroencephalographic activity assessed by BIS during sedation with sevoflurane. This was the first study using BIS with a sevoflurane sedation strategy [29]. We found a moderate correlation between MAC or FeSevo and BIS values. We also found a moderate correlation between RASS levels and BIS values. In a ROC analysis, BIS was able to predict deep sedation with an AUC of 0.84 and the optimal threshold was 72. However, the spread of BIS values was ranging from 24 up to 98 with false negative and false positive case in 21% and 18%, respectively. Previous studies tried to find a correlation between BIS and sedation scale using different sedative strategies without any success [30–32]. However, those results must be interpreted with caution. Indeed, BIS level is known to be influenced by muscular activity and neuromuscular blockade administration was associated with a decrease of BIS level especially during moderate sedation [33]. Yet, the French guideline on sedation in ICU recommended to use BIS only in case of neuromuscular blockade infusion [34]. Our results with sevoflurane confirm

the previous study and support the use of BIS measurement without neuromuscular blockade administration in ICU.

This study has some limitations. First, there were only 30 patients with a large age spread, which limits the result of FeSevo. A larger cohort may have been beneficial. However, the study was designed to optimise recruitment capacity. Second, patients were included away from the acute phase and admission with a RASS of 0 at inclusion, even under mechanical ventilation. This may not represent typical severe patients with several organ dysfunctions. Furthermore, due to the study design, there was no patient with current indication for deep sedation, especially patients with ARDS, who would benefit most from the administration of sevoflurane.

Clinical implications: Targeting a FE sevoflurane around 0.8% guarantees a deep sedation for all patients. Sevoflurane allows a quick and deep sedation that could be started just after induction of anaesthesia and tracheal intubation in ICU. This is useful for patients under neuromuscular blockage or at the beginning of sedation. Following this initial target, sevoflurane infusion may be adapted according to RASS score or BIS level when clinical scales are useless. Therefore, using volatile agents could probably decrease the requirement and doses of IV sedative.

CONCLUSIONS

MAC-DS seems to be of particular value to achieve sedation level in intensive care unit when sedation scales are unusable. MAC-DS₉₅, end-tidal concentration of sevoflurane to get 95% of patients in deep sedation, determined over more than 500 observations is achieved at 0.8% of expired fraction of sevoflurane.

LIST OF ABBREVIATIONS

ARDS: Acute respiratory distress syndrome

AUC: Area under the curve

BIS: Bispectral Index

BPS: Behavioural Pain Scale

FeSevo: Sevoflurane expiratory fraction

FiO₂: Fraction of inspired Oxygen

IC₉₅: 95% confidence interval

ICU: Intensive care unit

IQR: Interquartile range 25-75%

MAC: Minimal alveolar concentration

MAC-*DS*: Minimal alveolar concentration for deep sedation

PaO₂: Partial pressure of oxygen in arterial blood

PEEP: Positive End Expiratory Pressure

RASS: Richmond Assessment Sedation Score

ROC: Receiver operating characteristics

SAPS II: Simplified acute physiology score II

SOFA: Sequential Organ Failure Assessment score

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the “Institutional Review Board of Clermont-Ferrand, France” (N°EudraCT 2014-000759-10) and registered on *clinicaltrials.gov* (NCT 02202720). Written informed consent was obtained from patients or their relatives before study inclusion.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

JMC reports personal fees and non-financial support from Drager, GE Healthcare, Sedana Medical, Baxter, and Amomed; personal fees from Fisher and Paykel Healthcare, Orion, Philips Medical, and Fresenius Medical Care; and non-financial support from LFB and Bird Corporation, outside of the submitted work.

All other authors declare that they have no competing interests.

Funding

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Authors' contributions

All authors have done substantial contributions to conception and design. SP collected, analysed and interpreted the data. FB, CL and BP analysed and interpreted the data. FB was the main writer of the manuscript. JMC, TG, AJ, FV and JEB made important intellectual contributions to the manuscript. All authors read and approved the final manuscript.

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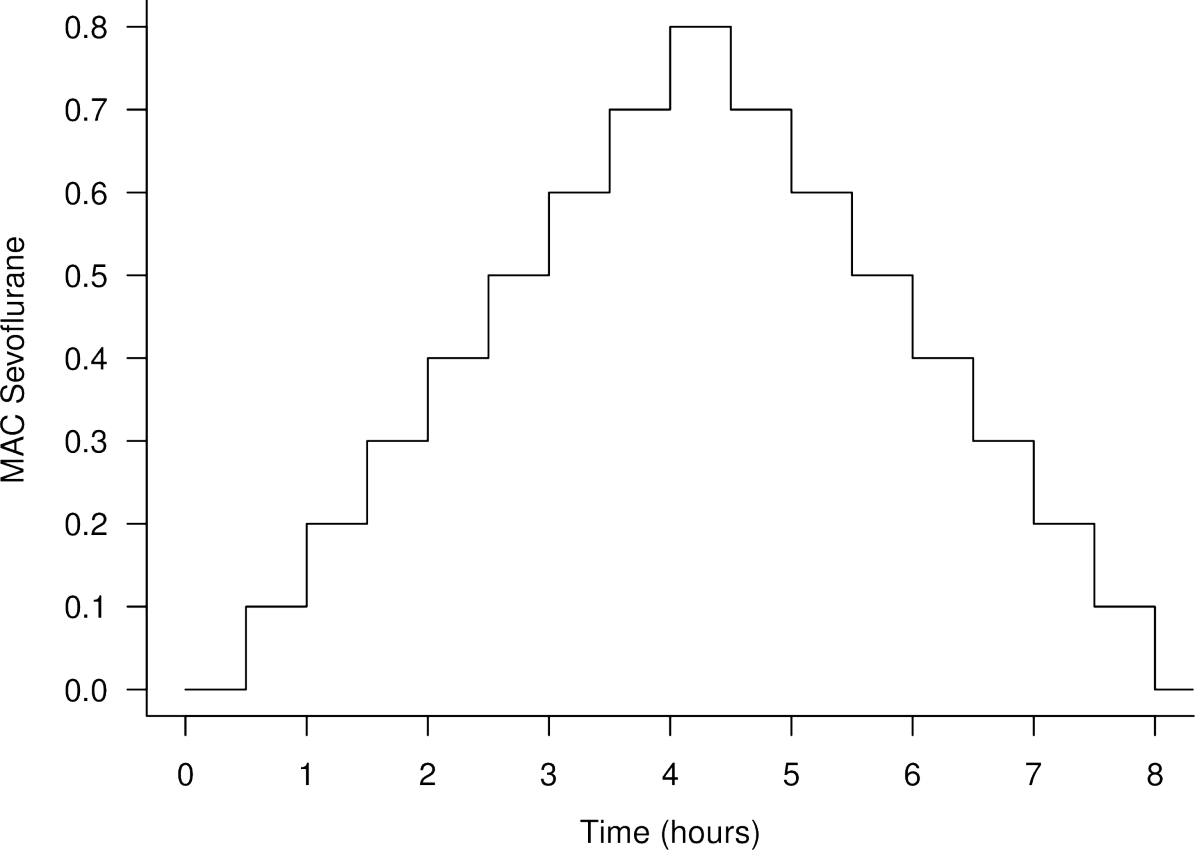
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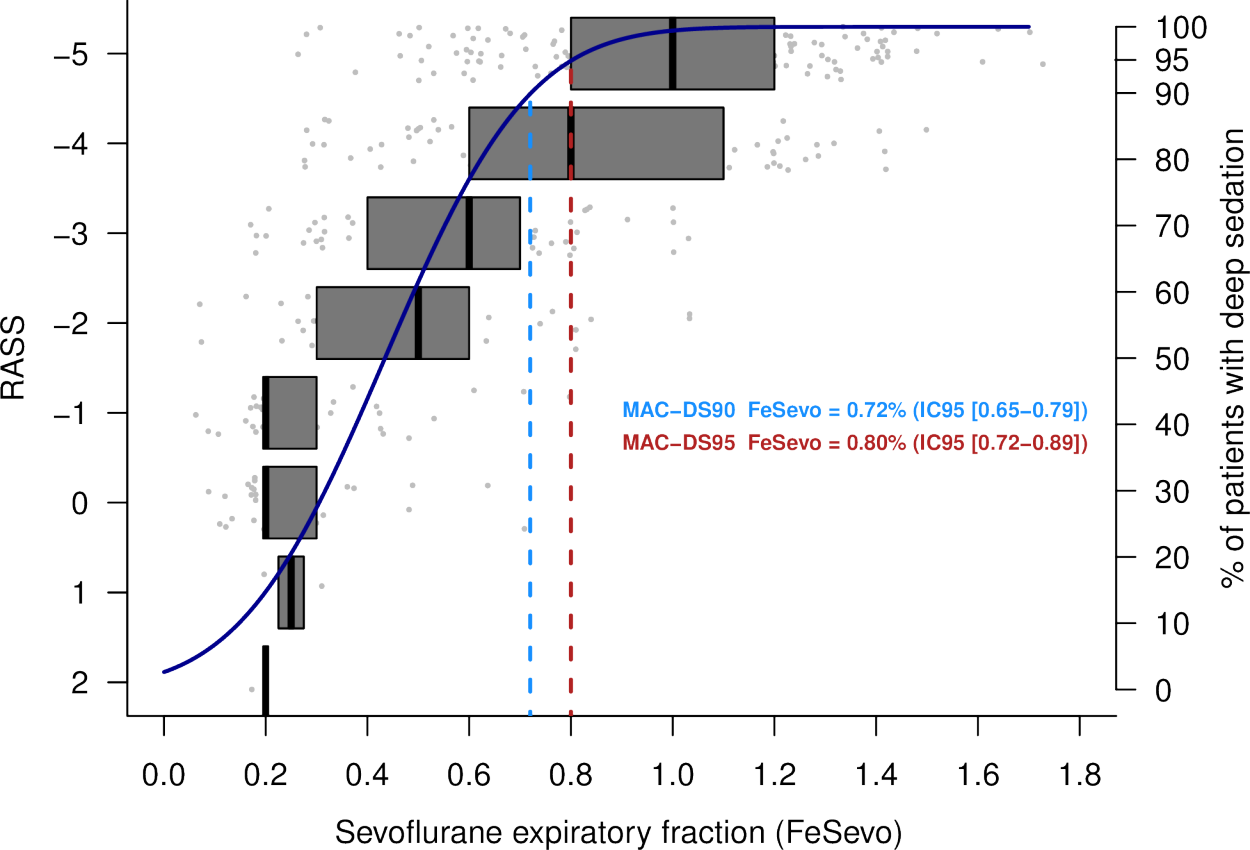
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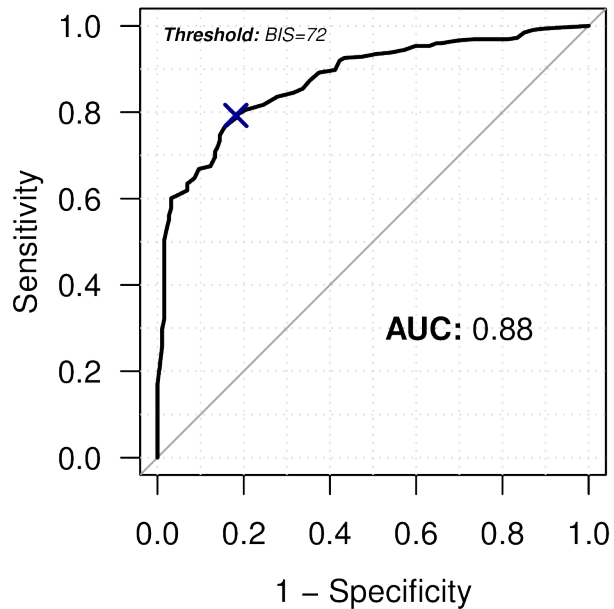
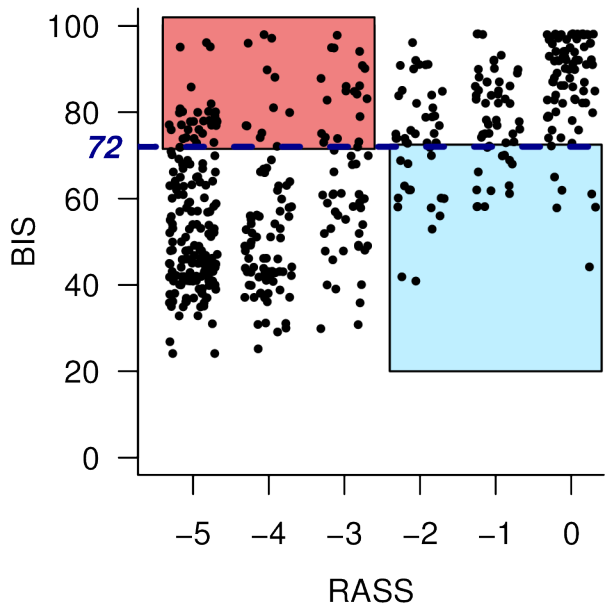
Figure 1: Study design: Evolution of the Minimal Alveolar Concentration (MAC) of Sevoflurane over time. Sevoflurane was started after inclusion, and the targeted MAC of Sevoflurane was stepwise increased by 0.1 MAC each 30 minutes from MAC 0 to MAC 0.8. After reaching MAC 0.8, Sevoflurane concentrations were decreased using the same steps that above. Richmond Assessment Sedation Score and other relevant information were collected fifteen minutes after at each stepwise

Figure 2: Minimal alveolar concentration of Sevoflurane (MAC Sevoflurane) to get a deep sedation (MAC-DS) as a Sevoflurane expiratory fraction (FeSevo). MAC-DS₉₀ and MAC-DS₉₅ represent the minimal Sevoflurane end-tidal concentration (express FeSevo) to reach 90% and 95% of deeply sedated patients respectively. MAC-DS₉₀ is achieved with a FeSevo of 0.72%. MAC-DS₉₅ is achieved with a FeSevo of 0.80%. Median values of FeSevo are shown by black segments for each Richmond Assessment Sedation Score levels (RASS). Grey box represents the interquartile range (25-75%) of FeSevo for each RASS levels. Blue curve represents the percentage of patient in deep sedation (RASS = -3, -4 or -5) for each FeSevo. IC95: 95% confidence interval.

Figure 3: Receiver operating characteristics curve of Bispectral index (BIS) (A) and distribution of BIS over Richmond Assessment Sedation Score (RASS) (B) The area under curve (AUC) was 0.88 with optimal cutoff at 72 leading to a sensitivity and specificity of 0.79 (95% confidence interval (IC95) [0.74-0.84]) and 0.82 (IC95 [0.76-0.87]) respectively. Positive and negative likelihood ratios were 3.15 and 0.24 respectively. There was a moderate correlation between RASS levels and BIS values ($r=0.63$, $p < 0.001$). Red square in B represent patients in deep sedation with a BIS over 72 ($n = 67$; 21%). Blue square represents patients with a BIS beneath 72 but not in deep sedation ($n = 34$; 18%).





A**B**

1 **Table 1:** Demographic and clinical baseline characteristics of the patients

Variable	All cohort (n = 30)
Age, year, median [IQR]	60 [47-69]
Males, n (%)	19 (63%)
Body mass index, kg/m ² , median [IQR]	26.7 [22.5-30.0]
ADMISSION	
Medical admission, n (%)	11 (37%)
Surgical admission, n (%)	19 (63%)
SAPS II, median [IQR]	31 [25-35]
SOFA, median [IQR]	6 [3-8]
RESPIRATORY CHARACTERISTICS	
Pressure support mode, n (%)	30 (100%)
PaO ₂ /FiO ₂ , median [IQR]	251 [206-344]
FiO ₂ , %, median [IQR]	30 [25-39]
Pressure support, cmH ₂ O, median [IQR]	9 [8-10]
PEEP, cmH ₂ O, median [IQR]	8 [7-10]
NEUROLOGICAL CHARACTERISTICS	
RASS, median [IQR]	0 [0-0]

BPS, median [IQR]	3 [3-3]
Bispectral Index, median [IQR]	93 [79-97]
Remifentanyl infusion, n (%)	21 (60%)
Remifentanyl infusion rate, $\mu\text{g}/\text{kg}/\text{min}$, median [IQR]	0.09 [0.03-0.10]

HEMODYNAMIC CHARACTERISTICS

Heart rate, beats per minutes, median [IQR]	97 [76-107]
Mean arterial pressure, mmHg, median [IQR]	92 [76-103]
Norepinephrine infusion, n (%)	8 (27%)
Norepinephrine infusion rate, $\mu\text{g}/\text{kg}/\text{min}$, median [IQR]	0.10 [0.04-0.15]

OUTCOMES

Mechanical ventilation duration, days, median [IQR]	5 [1-22]
ICU length of stay, days, median [IQR]	13 [5-29]

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- 2 BPS: Behavioural Pain Scale, FiO₂: Fraction of inspired Oxygen, IQR: Interquartile range 25-
 - 3 75%, ICU: Intensive Care Unit, PaO₂: Partial pressure of oxygen in arterial blood, PEEP:
 - 4 Positive End Expiratory Pressure, RASS: Richmond Assessment Sedation Score, SAPS II:
 - 5 Simplified acute physiology score II, SOFA: Sequential Organ Failure Assessment score