Feasibility of Anesthesia Maintenance With Sevoflurane During Cardiopulmonary Bypass:
A Pilot Pharmacokinetics Study

Roberta Meroni, MD, Stefano Gianni, MD, Marcello Guarnieri, MD, Francesco Saglietti, MD, Marco Gemma, MD, Alberto Zangrillo, MD, Elena Bignami, MD

Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

Objective: Adequate maintenance of hypnosis during anesthesia throughout surgery using sevoflurane alone was investigated. In addition, sevoflurane pharmacokinetics during cardiopulmonary bypass were analyzed.

Design: This was a pilot pharmacokinetic study.

Setting: Tertiary care university hospital.

Participants: The study comprised 10 patients aged between 18 and 75 years who underwent elective mitral valve surgery.

Interventions: The end-tidal and sevoflurane plasma concentrations were measured throughout cardiac surgery procedures involving cardiopulmonary bypass. The sevoflurane plasma concentration was measured using gas chromatography. In addition, the ratio between sevoflurane alveolar concentration and inspired concentration over time (FA/FI) was analyzed to describe wash-in and wash-out curves.

Measurements and Main Results: Hypnosis was maintained adequately throughout surgery using sevoflurane alone. The bispectral index was maintained between 40 and 60 during cardiopulmonary bypass. The end-tidal sevoflurane was significantly different before and during cardiopulmonary bypass (1.86% ± 0.54% vs 1.30% ± 0.58%, respectively; p < 0.001). However, the sevoflurane plasma concentration was not significantly different before and after cardiopulmonary bypass start-up (40.55 µg/mL [76.62-125.33] before cardiopulmonary bypass and 36.24 µg/mL [56.49-81.42] during cardiopulmonary bypass). This mismatch possibly can be explained by changes that occurred after cardiopulmonary bypass start-up, such as reductions of body temperature (36.33 °C ± 0.46 °C vs 32.98 °C ± 2.38 °C, respectively; p < 0.001) and hematocrit (35.62% ± 3.98% vs 25.5% ± 3.08%, respectively; p < 0.001). The sevoflurane alveolar concentration varied according to sevoflurane plasma concentration and bispectral index values. No adverse events regarding sevoflurane administration during cardiopulmonary bypass were observed.

Conclusions: Sevoflurane end-tidal values were reliable indicators of adequate anesthesia during all cardiac surgery procedures involving cardiopulmonary bypass.

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Key Words: sevoflurane; kinetics; bispectral index; cardiopulmonary bypass; anesthesia

EVERY YEAR, MORE than 1 million patients undergo cardiac surgery.¹ Despite improvements in perioperative management, morbidity and mortality still are commonplace.

Several randomized controlled trials (RCTs) and meta-analyses suggested that volatile anesthetic use in cardiac surgery (in particular sevoflurane and desflurane), mimicking ischemic preconditioning, might reduce perioperative myocardial damage and postoperative mortality.²⁻¹³

Some authors¹⁴ suggested that volatile anesthetic administration throughout surgery appeared to provide superior protective effects compared with administration only before
or after cardiopulmonary bypass (CPB). Moreover, these protective effects seemed to be related to the amount of volatile anesthetics administered.\textsuperscript{11} These data confirmed that volatile anesthetic administration during coronary artery bypass graft surgery certainly is advantageous; therefore, it would be extremely interesting to identify the anesthetic regimen necessary to reduce perioperative morbidity and mortality.

To reach better levels of myocardial protection, precise and homogenous protocols for drug administration are necessary. According to these findings, an anesthetic plan based on the monophasic pharmacologic maintenance of general anesthesia with volatile agents might be a useful option for cardiac anesthesiologists. Cardiac surgery, however, is a setting that presents a high risk of intraoperative awareness,\textsuperscript{15} and the feasibility of halogenated monophasic pharmacologic maintenance during CPB needs to be assessed. Anesthesia maintenance during CPB is challenging due to modifications in systemic blood flow (nonpulsatile blood flow), hypothermia, and hemodilution, with important changes in pharmacodynamics and pharmacokinetics.\textsuperscript{16,17} In addition, the oxygenator and CPB circuit can bind different amounts of drugs administered to the patient, and hypothermia itself can lead to reduced consciousness, causing a change in anesthetic requirements during CPB.\textsuperscript{17} To date, few studies have described volatile anesthetic complete kinetics in vivo during CPB.\textsuperscript{18–25} Anesthetic wash-in is slower during the cooling phase, whereas wash-out during the rewarming phase is more similar to in vivo–model wash-out. Moreover, the degradation product hexafluoroisopropanol (HFIP) is a poorly studied molecule with implications in sevoflurane kinetics that are not understood fully.\textsuperscript{26}

During the hypothermic phase there are increases in the blood/gas solubility coefficient and tissue capacity for halogenated anesthetics, leading to slower induction of and emergence from general anesthesia.\textsuperscript{27} Several studies have underlined a decrease in anesthetic requirements during the hypothermic phase of CPB.\textsuperscript{18–25} Despite these findings, feasibility of the monophasic pharmacologic maintenance of general anesthesia with sevoflurane alone still is a matter of debate.

The primary endpoint of this pilot study was to evaluate the adequate maintenance of hypnosis during general anesthesia using sevoflurane as the only hypnotic agent throughout surgery, including CPB. Sevoflurane administration was titrated to maintain a constant and adequate level of bispectral index (BIS) between 40 and 60. Moreover, the authors defined the basis of sevoflurane pharmacokinetics during CPB.

**Methods**

**Study Population**

After receiving ethics committee approval, 10 consecutive patients were enrolled in the study. Written informed consent was obtained before surgery. Patients of both sexes aged between 18 and 75 years with good cardiac function (ejection fraction > 50% or end-diastolic diameter < 65 mm) who underwent elective mitral valve surgery (mitral valve replacement or mitral valve repair) with median sternotomy were included. Exclusion criteria were poor cardiac function (ejection fraction < 50% or end-diastolic diameter > 65 mm); coronary artery disease; diabetes mellitus; renal (serum creatinine > 1.5 mg/dL) or hepatic disease; use of angiotensin-converting enzyme inhibitors and sedative drugs (such as benzodiazepines); and a history of alcoholism.

**Anesthetic Management**

One hour before surgery all patients received intramuscular morphine (0.1 mg/kg) and scopolamine (0.25 mg) premedication. Standard intraoperative monitoring was performed, including electrocardiography, invasive arterial blood pressure, central venous pressure, pulse oximetry, capnography, vesical, temperature, and urine output. BIS was started before the induction of general anesthesia and was used to monitor sedation levels throughout surgery.\textsuperscript{15}

General anesthesia was induced with fentanyl (3 μg/kg), sodium thiopental (3–5 mg/kg), and rocuronium (0.6–1 mg/kg) or succinylcholine (1 mg/kg) when required. After a BIS index value of < 60 was reached, patients underwent orotracheal intubation with a cuffed tube. After intubation, volume-controlled ventilation was applied with a Primus ventilator (Dräger, Lübeck, Germany) using an oxygen/air mixture and high fresh gas flows (> 8 L/min) to prevent rebreathing of the exhaled mixture (ventilator settings: tidal volume 8 mL/kg; fraction of inspired oxygen < 0.8; positive end-expiratory pressure 0; and respiratory rate titrated to avoid hypercapnia). Anesthesia was maintained using inhaled sevoflurane (Sevorane; Abbott, Abbott Park, IL; starting dose 1 end-tidal minimum alveolar concentration, equal to 2%); rocuronium bromide via continuous infusion (30–50 mg/h); and fentanyl boluses when needed. Maintenance was carried out throughout surgery using sevoflurane administered through a vaporizer (Vapor 2000; Dräger). Intraoperative administration of sevoflurane was titrated to keep the BIS level between 40 and 60\textsuperscript{15} to obtain an adequate level of sedation.

Throughout surgery, hemodynamics were modified using vasopressors when necessary. Hemodynamic data, BIS level, and inspired and end-tidal sevoflurane concentrations were monitored and collected before induction and after 5, 10, 15, 20, 25, and 30 minutes. Blood samples were collected to perform arterial blood gas analysis and to evaluate the plasma concentration of sevoflurane and HFIP before induction and after 10, 20, and 30 minutes. Heparin (300 U/kg) was administered to patients before CPB to maintain an activated clotting time > 480 seconds. CPB was performed using the Affinity oxygenator (Medtronic, Minneapolis, MN) and Medtronic circuit. Mechanical ventilation was discontinued after CPB start, which then was carried out using moderate hypothermia (32–34°C). Myocardial protection during aortic cross-clamping was provided by antegrade and/or retrograde cold blood cardioplegia.

During CPB, fresh gas flow was adjusted to maintain acid-base balance. Sevoflurane administration was provided through a vaporizer (Vapor 2000) linked to a CPB oxygenator.
to maintain a constantly adequate BIS level (40-60).\textsuperscript{15} Hemodynamic data, BIS level, and inspired and end-tidal sevoflurane concentrations were monitored and collected every 5 minutes throughout CPB. Blood samples were collected every 10 minutes to perform arterial blood gas analysis and evaluate hematic sevoflurane and HFIP concentrations. HFIP is the most important degradation product of sevoflurane metabolism, and it is important to better assess sevoflurane kinetics. During CPB, sevoflurane gas concentration was sampled using a gas analyzer connected to the inspiratory and expiratory ports of the oxygenator. Sampling on the expiratory port required previous discontinuation of the aspiration of exhaled gas. Mean arterial blood pressure was maintained between 60 and 80 mmHg, hypotension was corrected using vasopressors, whereas hypertension was controlled using vasodilators when necessary. At the end of CPB, mechanical ventilation was resumed. Up to the end of surgery, anesthesia was maintained with sevoflurane alone; administration continued to be titrated against the BIS value. Hemodynamic data, BIS level, inspired and end-tidal sevoflurane concentrations, and blood samples also were collected at CPB weaning and at the end of surgery.

After surgery, patients (sedated with propofol) were transferred to the intensive care unit (ICU). Hemodynamic data and blood samples were collected 24 hours after surgery to perform arterial blood gas analysis and to evaluate plasma concentration of sevoflurane and HFIP.

Gas Chromatography Analysis

Arterial blood samples for gas chromatography were collected in Vacutainer tubes (3-4 mL). Probes were centrifuged for 15 minutes, and plasma supernatant was frozen at −20°C.

Samples were analyzed using gas chromatography mass spectrometry (4000 GC-MS/MS Varian; Agilent Technologies, Santa Clara, CA) to measure sevoflurane and HFIP. The authors created a calibration curve using Sevorane (Abbott) and 1,1,1,3,3,3-hexafluoride-2-propanol (Sigma-Aldrich, St. Louis, MO). Solutions were diluted in dimethyl sulphoxide. A calibration curve was obtained by diluting the solution in serum to values of 100, 50, 20, 10, 5, 2, and 1 μg. To measure sevoflurane (μg) and HFIP (μg), 400 μL of every sample were analyzed. Free fractions of HFIP (not the glucoronate type) were dosed.

Sample Size Calculation

Sample size calculation was performed as follows. The authors predicted a BIS variation with a confidence interval of 45 to 55, an alpha error of 0.5, and a power of 0.8. The authors calculated a sample size of 8 patients but planned to include 10 patients to take into account a possible non-normality of the distribution.

Statistical Analysis

Data were analyzed using Stata 11.1 software (StataCorp, College Station, TX). No imputations were applied for missing data. Data are presented as medians (25th and 75th percentiles) or as means (± standard deviation [SD]). Means and SDs were used when the variables were normally distributed, whereas medians and interquartile ranges were used with non-normally distributed variables. Dichotomous data were compared with the 2-tailed chi-square test, Yates correction, or Fisher exact test when appropriate. Continuous measurements were compared using the Mann-Whitney U test.

Results

Ten patients (5 males and 5 females) were included in this study. The population was homogenous for preoperative characteristics, surgical procedure, and surgical risk. The preoperative characteristics of the study population are shown in Table 1.

All patients underwent mitral valve repair. Surgery lasted 189 ± 32.3 minutes (CPB and aortic clamp lasting 89.1 ± 27.3 min and 70.6 ± 25.6 min, respectively). During surgery the following physiologic parameters that generally undergo significant variation during CPB were monitored: mean arterial pressure, temperature, hematocrit, pH, and glycemia (Table 2). There was no episode of intraoperative or postoperative mortality, nor were there episodes of postoperative myocardial infarction or low-cardiac-output syndrome during ICU stay.

During the initial postoperative period (especially during the first 6-12 h), 9 patients needed low-dose inotropic support (dopamine, 5 μg/kg/min). Inotropic support was discontinued before ICU discharge. Four patients developed postoperative supraventricular arrhythmias, which were controlled effectively with antiarrhythmic drugs or temporary pacing. In the intraoperative period 3 patients needed inotropic support with epinephrine (dose 0.03-0.1 μg/kg/min), which was changed to dopamine at the end of the surgical procedure. One patient needed norepinephrine (0.03 μg/kg/min) to treat intraoperative hypotension.

Mean ICU stay was 1.5 days (SD 0.8 days). Mean hospital stay was 10.5 days (SD 3.44 days).

BIS Monitoring

On entering the operating room, the BIS level was 95.5 ± 3.6. After induction of general anesthesia, BIS

| Table 1 Summary of Anthropometrics of Study Population |
|---------------------------------|------------------|
| Anthropometrics                  | Mean ± SD        |
| Age (yr)                        | 53.3 ± 10.49     |
| Weight (kg)                     | 73.8 ± 12.61     |
| Height (cm)                     | 169.8 ± 8.66     |
| BMI (kg/cm²)                    | 25.46 ± 3.09     |
| Preoperative TEE                |                 |
| EF (%)                          | 64.4 ± 6.1       |
| EDD (mm)                        | 56.7 ± 5.92      |
| SPP (mmHg)                      | 32.71 ± 4.74     |
| IVS (mm)                        | 10.37 ± 0.9      |

Abbreviations: BMI, body mass index; EDD, end-diastolic diameter; EF, ejection fraction; IVS, interventricular septum; SPP, systolic pulmonary pressure (estimated using echocardiography); TEE, transesophageal echocardiography.
descended rapidly and reached the target level between 40 and 60. After induction, BIS monitoring reached steady state, and the value was maintained between 40 and 60 constantly, meaning the sedation level was constant throughout surgery. During CPB, the BIS level was maintained between the target values of 40 and 60. Statistical analysis suggested that BIS values did not differ when comparing those before CPB with those during CPB (mean values 42.34 \pm 8.76 and 36.37 \pm 7.50, respectively; p = 0.005).

**End-Tidal Sevoflurane**

End-tidal sevoflurane levels during surgery also were monitored. Sevoflurane administration was titrated to the BIS level and matched the anesthetic requirement during different surgical periods. Changes in anesthetic requirement later were correlated to different types of surgical stimulation. Details of end-tidal sevoflurane plasma concentration and BIS are shown in Fig 1 and Table 3.

During the period before CPB, an appropriate BIS level was guaranteed by administering a mean amount of end-tidal sevoflurane of 1.86%. The mean value of end-tidal sevoflurane during CPB was 1.3%, demonstrating a reduction of anesthetic requirement during CPB. Statistical analysis suggested the difference in end-tidal sevoflurane, comparing the mechanical ventilation stage with CPB, to be significant (1.86 \pm 0.54 vs. 1.30 \pm 0.58, respectively; p < 0.001). The difference in the inspiratory amount of administered sevoflurane was significant when comparing the pre-CPB stage with CPB (2.25 \pm 0.65 vs. 1.94 \pm 0.71; p = 0.016).

**Sevoflurane Concentration**

Figure 1 illustrates the details of sevoflurane plasma concentration levels throughout surgery.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before CPB</th>
<th>During CPB</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>72 \pm 20</td>
<td>61 \pm 18</td>
<td>0.005</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.3 \pm 0.4</td>
<td>32.9 \pm 2.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 \pm 0.06</td>
<td>7.42 \pm 0.07</td>
<td>0.4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35.6 \pm 3.9</td>
<td>25.5 \pm 3.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>96 \pm 18</td>
<td>145 \pm 46</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BIS</td>
<td>50 \pm 33</td>
<td>38 \pm 7</td>
<td>0.06</td>
</tr>
<tr>
<td>Sevoflurane end-tidal (%)</td>
<td>1.86 \pm 0.54</td>
<td>1.30 \pm 0.58</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>F/I sevoflurane (%)</td>
<td>2.2 \pm 0.6</td>
<td>1.94 \pm 0.71</td>
<td>0.016</td>
</tr>
<tr>
<td>F/A/Fi ratio</td>
<td>0.83 \pm 0.08</td>
<td>0.67 \pm 0.22</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sevoflurane concentration (µg/mL)</td>
<td>76.62 (40.55-125.33)</td>
<td>56.49 (36.24-81.42)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

NOTE. Data are expressed as mean ± standard deviation or median (25th-75th). Abbreviations: BIS, bispectral index; CPB, cardiopulmonary bypass; F/A, alveolar sevoflurane (end-tidal) concentration; F/I, inspired sevoflurane concentration.

During CPB, the sevoflurane plasma value varied greatly from patient to patient and among different blood samples taken from the same patient. Despite these differences, the BIS level always was adequate in every patient during CPB.

When CPB was started, the sevoflurane plasma value decreased because of an end-tidal sevoflurane decrease. After this, the sevoflurane plasma value increased progressively, reaching its peak approximately 35 to 40 minutes after CPB start. The BIS level decreased in correspondence with the increase in anesthetic plasma concentration. Despite this trend, the sevoflurane concentration was not significantly different before and after CPB start (76.62 [40.55-125.33] before CPB and 56.49 [36.24-81.42] after CPB start).

The final stage of CPB and its discontinuation corresponded to decreases in sevoflurane plasma and end-tidal sevoflurane and an increase in BIS level. Upon CPB discontinuation and the restart of mechanical ventilation, sevoflurane plasma increased once again until the end of surgery. During the first postoperative day, the sevoflurane plasma level progressively decreased.

**F/A/Fi Ratio**

The F/A/Fi ratio also was evaluated (F/A is alveolar [end-tidal] concentration and F/I is inspired concentration) (Fig 2). The F/A/Fi ratio initially was evaluated at fixed time points during the first 30 minutes of mechanical ventilation and then during the first 30 minutes of CPB.

During the first 30 minutes of mechanical ventilation, the sevoflurane wash-in curve demonstrated a steep increase of F/A/Fi ratio, reaching steady state after approximately 25 minutes. The mean value of the F/A/Fi ratio at steady state was 0.83 \pm 0.08.

Later, the sevoflurane wash-in curve during the first 30 minutes of CPB was evaluated, after the discontinuation of mechanical ventilation and the beginning of sevoflurane
administration through the membrane oxygenator. The \( F_A/F_I \) ratio had a starting value of approximately 0.5 because sevoflurane already had been administered before CPB start. During the initial minutes, the \( F_A/F_I \) ratio increased progressively, although in a slower manner when compared with the previously described curve. Steady state was reached approximately 25 minutes after CPB start. The \( F_A/F_I \) ratio at steady state had a mean value of 0.67 ± 0.22.

**Hexafluoroisopropanol**

To better understand sevoflurane metabolism, HFIP, a product of degradation of sevoflurane, was measured throughout the procedure at the same time that sevoflurane concentration was measured. HHFIP hematic concentration rose slightly after the sevoflurane peak concentration (with a latency period of 20 min). HFIP variations throughout surgery are

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**Table 3**

<table>
<thead>
<tr>
<th>Time Points (min)</th>
<th>Sevoflurane Inspired Fraction (%)</th>
<th>End-Tidal Sevoflurane (%)</th>
<th>Sevoflurane Plasma Concentration (µg/mL)</th>
<th>HFIP (µg/mL)</th>
<th>BIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA induction</td>
<td>2.5 ± 0.5</td>
<td>1.3 ± 1.1</td>
<td>0.20 ± 0.26</td>
<td>0 ± 0</td>
<td>95 ± 3.5</td>
</tr>
<tr>
<td>10</td>
<td>2.3 ± 0.7</td>
<td>1.6 ± 1.3</td>
<td>84.60 ± 56.58</td>
<td>0.04 ± 0.09</td>
<td>44 ± 6.6</td>
</tr>
<tr>
<td>20</td>
<td>2.2 ± 0.7</td>
<td>1.9 ± 1.4</td>
<td>128.17 ± 96.49</td>
<td>0.26 ± 0.26</td>
<td>39 ± 4.8</td>
</tr>
<tr>
<td>30</td>
<td>2.0 ± 0.6</td>
<td>1.7 ± 1.3</td>
<td>88.97 ± 38.04</td>
<td>0.30 ± 0.22</td>
<td>37 ± 4.7</td>
</tr>
<tr>
<td>40</td>
<td>1.6 ± 0.7</td>
<td>1.8 ± 1.3</td>
<td>109.06 ± 46.78</td>
<td>0.32 ± 0.20</td>
<td>36 ± 6.2</td>
</tr>
<tr>
<td>CPB start</td>
<td>1.8 ± 0.7</td>
<td>1.1 ± 1.1</td>
<td>38.54 ± 20.05</td>
<td>0.33 ± 0.14</td>
<td>43 ± 8.9</td>
</tr>
<tr>
<td>Cross-clamp</td>
<td>1.9 ± 0.7</td>
<td>1.2 ± 1.1</td>
<td>49.83 ± 23.77</td>
<td>0.38 ± 0.16</td>
<td>39 ± 5.7</td>
</tr>
<tr>
<td>5</td>
<td>1.9 ± 0.9</td>
<td>1.2 ± 1.1</td>
<td>69.60 ± 61.08</td>
<td>0.34 ± 0.16</td>
<td>39 ± 8.2</td>
</tr>
<tr>
<td>10</td>
<td>2.0 ± 0.7</td>
<td>1.5 ± 1.2</td>
<td>79.08 ± 50.98</td>
<td>0.34 ± 0.12</td>
<td>39 ± 7.2</td>
</tr>
<tr>
<td>20</td>
<td>2.1 ± 0.6</td>
<td>1.4 ± 1.2</td>
<td>82.51 ± 35.51</td>
<td>0.30 ± 0.11</td>
<td>40 ± 7.3</td>
</tr>
<tr>
<td>30</td>
<td>2.2 ± 0.7</td>
<td>1.6 ± 1.3</td>
<td>93.09 ± 55.83</td>
<td>0.32 ± 0.11</td>
<td>39 ± 4.7</td>
</tr>
<tr>
<td>40</td>
<td>1.9 ± 0.5</td>
<td>1.5 ± 1.2</td>
<td>100.02 ± 66.58</td>
<td>0.33 ± 0.12</td>
<td>34 ± 4.8</td>
</tr>
<tr>
<td>50</td>
<td>1.9 ± 0.4</td>
<td>1.4 ± 1.2</td>
<td>86.49 ± 66.03</td>
<td>0.41 ± 0.20</td>
<td>38 ± 9.5</td>
</tr>
<tr>
<td>60</td>
<td>1.8 ± 0.5</td>
<td>1.6 ± 1.3</td>
<td>57.32 ± 22.22</td>
<td>0.39 ± 0.15</td>
<td>39 ± 1.4</td>
</tr>
<tr>
<td>70</td>
<td>1.9 ± 0.5</td>
<td>1.5 ± 1.2</td>
<td>38.31 ± 5.17</td>
<td>0.40 ± 0.14</td>
<td>35 ± 2.5</td>
</tr>
<tr>
<td>85</td>
<td>1.8 ± 0.3</td>
<td>1.6 ± 1.3</td>
<td>36.33 ± 0.23</td>
<td>0.39 ± 0.15</td>
<td>37 ± 5.3</td>
</tr>
<tr>
<td>90</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 1.2</td>
<td>92.03 ± 78.14</td>
<td>0.39 ± 0.16</td>
<td>45 ± 5.5</td>
</tr>
<tr>
<td>End of surgery</td>
<td>0 ± 0</td>
<td>0 ± 0.0</td>
<td>72.71 ± 58.21</td>
<td>0.4 ± 0.14</td>
<td>42 ± 6.7</td>
</tr>
</tbody>
</table>

**NOTE.** Data are presented as mean ± standard deviation.

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Fig 2. \( F_A/F_I \) changes over time, before and during cardiopulmonary bypass. \( F_A \), alveolar sevoflurane (end-tidal) concentration; \( F_I \), inspired sevoflurane concentration CPB, cardiopulmonary bypass; poli, a mathematic function.
summarized in Table 3 and Figure 3. HFIP 24 hours after surgery was 0.21 ± 0.20 (data presented as mean ± SD).

**Discussion**

**BIS Monitoring**

The primary endpoint of this study was the feasibility of maintaining general anesthesia with sevoflurane as the only hypnotic agent throughout surgery, especially during CPB. For this reason, the BIS level was used to monitor the depth of hypnosis throughout the entire procedure, with volatile anesthetic administration titrated against it. These data confirmed the possibility of maintaining an adequate level of general anesthesia throughout surgery, especially during CPB, by administering sevoflurane alone. Although the BIS level was maintained within the desired values throughout surgery, the BIS value was observed to increase when shifting from mechanical ventilation to CPB and vice versa. These data, although not statistically significant, highlighted the concrete risk of anesthesia level lightening and intraoperative awareness during these moments of transition.

**End-Tidal Sevoflurane**

The next step was to evaluate changes in terms of anesthetic requirement (ie, end-tidal sevoflurane, moving from mechanical ventilation to CPB).

End-tidal sevoflurane rapidly increased immediately after induction. After 10 minutes, the level decreased due to reduced anesthetic requirement, given the lack of surgical stimulation during this stage. Sevoflurane requirements rose once again when surgery began, with the end-tidal value remaining constant up to aortic cannulation.

When CPB started, the end-tidal sevoflurane decreased once again; this decrease corresponded to an increase of BIS level, causing temporary instability when moving from mechanical ventilation to CPB. During CPB, sevoflurane was no longer administered through mechanical ventilation but was administered through the inlet port of the oxygenator.

The physiologic alveolar membrane was replaced by a membrane oxygenator. After complete establishment of CPB, end-tidal sevoflurane increased, maintaining a value inferior to that observed during mechanical ventilation. End-tidal sevoflurane was maintained at almost constant value during CPB, except for a brief reduction during the final period of CPB (30-35 minutes after CPB start). This reduction might have been due to a small, transient reduction of BIS level, observed immediately before end-tidal sevoflurane reduction. The BIS level guaranteed a constantly adequate level of hypnosis throughout CPB.

**Sevoflurane Concentration**

Immediately after induction, the sevoflurane plasma values increased for up to 20 minutes and then decreased after 30 minutes of mechanical ventilation in all patients, possibly due to interruptions in mechanical ventilation during sternotomy. During high-flow ventilation, brief interruptions of mechanical ventilation have been linked to fast anesthetic wash-out. An adequate BIS level guaranteed appropriate sedation depth in this stage. After sternotomy, the sevoflurane plasma value increased, briefly reaching presternotomy values. Plasma sevoflurane levels during CPB were lower than before CPB, following a pattern similar to the end-tidal concentration. In fact, a lower sevoflurane dose was needed to maintain a constantly adequate BIS level.

During weaning from CPB, sevoflurane plasma levels and end-tidal sevoflurane rose again, until the end of surgery. The reasons for this lower need for hypnotic may have been multifactorial. The lower body temperature, reducing cerebral metabolism, may have played a role. Moreover, many pharmacokinetic phenomena occur after CPB start, such as the sudden increase of distribution volume, and this observation needs additional research.

**$F_A/F_I$ Ratio**

The authors also sought to determine the definition of a sevoflurane wash-in curve during CPB and compare this curve with that described in the literature. The $F_A/F_I$ ratio was evaluated at fixed time points during the first 30 minutes of mechanical ventilation and then during the first 30 minutes of CPB because, according to the literature, volatile anesthetic kinetics reached steady state in about 30 minutes. The wash-in curve realized in the study presented here was very similar to that described by Yasuda et al in 1991. The $F_A/F_I$ ratio curve during CPB observed in the study presented here was similar to the pre-CPB curve, although the steady state was reached more slowly.

**General Considerations**

There is extensive evidence from RCTs and meta-analyses that volatile anesthetics, mimicking ischemic preconditioning, can protect the heart from cardiac surgery–related myocardial injury. Some evidence suggested that they might even reduce...
postoperative mortality. Moreover, the amount of volatile anesthetics administered throughout surgery has been demonstrated to be related positively to the cardioprotective effect. For safe administration in everyday clinical practice, it is paramount to define volatile anesthetic pharmacokinetics during CPB and to assess the dosage required to achieve adequate sedation during CPB, hence removing the risk of intraoperative awareness. To date, only a few studies have described sevoflurane pharmacokinetics during CPB, and the safety of monopharmacologic sevoflurane maintenance has not been demonstrated. To prevent intraoperative awareness, the pharmacokinetic and pharmacodynamic changes caused by CPB need to be assessed specifically for this drug. Moreover, no evidence is available concerning the efficacy of monopharmacologic sevoflurane maintenance during CPB. In fact, during CPB, the normal kinetics of volatile anesthetics are modified extensively.

According to Mets et al the effects of CPB on volatile anesthetic uptake mainly depended on the effects of CPB on the blood/gas solubility coefficient of volatile anesthetics (hypothermia that increases solubility and hemodilution that decreases it); increased tissue solubility due to hypothermia; uptake; and accumulation of anesthetics by the oxygenator and CPB circuit. Moreover, hypothermia increases tissue capacity for volatile anesthetics; together with increased solubility, this slows the rise of anesthetic partial pressure in arterial blood. Alterations in blood flow distribution (leading to reduced drug metabolism and elimination) and hypotension, both common during CPB, also might play a role, albeit a less critical one.

Cardiac surgery is a setting with a high risk of intraoperative awareness. Taken together, these modifications of sevoflurane pharmacokinetics lead to issues concerning effectiveness and safety. It has been shown that BIS monitoring of the anesthesia level decreased the incidence of hemodynamic instabilities caused by anesthetic overdose and enabled more precise titration of anesthetic agents during CPB. In particular, specific studies have shown that BIS-guided anesthesia significantly reduced the frequency of episodes of intraoperative awareness in patients at high risk of recollection. Consequently, the authors stress the need for intraoperative anesthesia monitoring to guarantee adequate sedation throughout surgery.

The authors found that monopharmacologic hypnosis maintenance during general anesthesia using sevoflurane alone throughout surgery was feasible and effective. This finding might be an important milestone in cardiac anesthesia. The next step would be to perform new studies to confirm outcome improvement with volatile-based anesthetics in cardiac surgery.

Limitations

The limitations of this study included the small number of patients enrolled, the inclusion of only low-risk patients, and the relatively small amount of information collected regarding the role of HFIP. Moreover, because data were limited to mitral valve surgery, the authors were able to draw conclusions only about this specific population and additional research is necessary to better describe sevoflurane kinetics in other settings. Mitral valve surgery was chosen to achieve a homogenous sample, with reference to surgical technique, CPB times, surgical risk, intraoperative blood loss, and incidence of complications. Finally, BIS monitoring still has some limitations. Falsey elevated (ie, significant electromyographic activity) and falsely lower BIS values are known to confound BIS interpretation (opioids).

Conclusions

These findings implied the need for a better understanding of volatile anesthetic kinetics during CPB and their actual role in myocardial protection. To achieve this, the authors underline the need for larger RCTs on this topic that probably will pave the way toward new cardioprotective anesthesia.

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