Anesthetic gas consumption with target-controlled administration versus a semi-closed circle system with automatic end-tidal concentration control in an artificial lung model

Martin Bellgardt1,2, Vladimir Vinnikov1, Adrian Iustin Georgevici1, Livia Procopiuc1, Thomas Peter Weber1, Andreas Meiser2, Jennifer Herzog-Niescery1, Dominik Drees1
1 Department of Anesthesiology and Intensive Care Medicine, St. Josef Hospital, Katholisches Klinikum Bochum, University Hospital, Ruhr-University of Bochum, Bochum, Germany
2 Department of Anesthesiology, Intensive Care Medicine and Pain Medicine, Saarland University Medical Centre, University of Saarland, Homburg/Saar, Germany
3 Paediatric Intensive Care Unit – Evelina London Children’s Healthcare, Guy’s and St. Thomas, NHS, London, UK

Abstract

The use of volatile anesthetics as sedatives in the intensive care unit is relevant to the patient’s outcome. We compared anesthetic gas consumption of the conventional semi-closed Aisys CS™ with the MIRUS™ system, which is the first anesthetic gas reflector system that can administer desflurane in addition to isoflurane and sevoflurane. We connected an artificial lung model to either a MIRUS™ system and a Puritan Bennett® 840 ventilator or an Aisys CS™ anesthesia machine. We found that consumption of 0.5% isoflurane, which corresponds to the target concentration 0.5 MAC, was averaged to 2 mL/h in the MIRUS™ system, which is identical to the Aisys CS™ at a fresh gas flow (FGF) of 1.0 L/min. MIRUS™ consumption of 1% sevoflurane was averaged to 10 mL/h, which corresponds to 8.4 mL/h at FGF 2.5 L/min. The MIRUS™ system consumed 3% or 4% desflurane at an average of 13.0 mL/h or 21.3 mL/h, which is between the consumption at 1.0 L/min and 2.5 L/min FGF. Thus, the MIRUS™ system can effectively deliver volatile anesthetics in clinically relevant concentrations in a similar rate as a conventional circular breathing system at FGFs between 1.0 L/min and 2.5 L/min.

Key words: anesthesia; circle system; consumption; desflurane; isoflurane; MIRUS; reflection; sevoflurane; volatile anesthetics; wash-out

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INTRODUCTION

Since the description of the circle system by Dräger and Roth in 1902, fresh gas flow (FGF) determined consumption and control of volatile agents.1 However, an alternative to the circle system – the reflection system – was described in 1989.2 In 2001, Enlund et al.3 described for the first time the use of the reflection method in clinical practice. One year later, the same authors published the use of such a device with 0.9% sevoflurane in a similar clinical setting. The consumption of this device correlated with that of a circle system with a FGF of 1.5 L/min.4

Currently, two devices using the reflection method are commercially available: (i) AnaConDa® (Sedana Medical, Danderyd, Sweden), and (ii) MIRUS™ (TIM, Koblenz, Germany).5,6 In addition, a small-volume AnaConDa® device with only 50 mL internal volume (AnaConDa®-S) instead of 100 mL in the previous model (AnaConDa®) was developed in order to reduce dead space. This miniaturization is expected to improve carbon dioxide dissipation but also to reduce anesthetic reflection. Indeed, we recently demonstrated that consumption of isoflurane and sevoflurane by both AnaConDa®-S and AnaConDa® is comparable to consumption of a circle system with a FGF of up to 1.0 L/min.7

Desflurane shows favorable kinetics, and it is less metabolized than sevoflurane.8,9 However, the low boiling point of desflurane makes its administration more challenging than administration of isoflurane or sevoflurane. Unlike the AnaConDa® devices, the MIRUS™ system can be used and is licensed for administration of desflurane.

The aim of this study was to compare consumption, enhancement, and release of isoflurane, sevoflurane, and desflurane in the MIRUS™ system versus the Aisys CS™ at FGF ranging between 0.5–5.0 L/min.

MATERIALS AND METHODS

Test lung

A plastic tank with a volume of 3.9 L (HPL 829, Lock & Lock, iSi Deutschland GmbH Solingen, Germany) served as a test lung. There were three ports on the upper lid of the tank. One port was connected with two bag valve units (volume 2 L each, accessory for Zeus™, Dräger Medical) via a Y-piece (6515-12-339-4401, Dräger Medical, Lübeck, Germany). The second port facilitated insufflation of carbon dioxide (AirLiquide Deutschland GmbH, Düsseldorf, Germany). The third port was connected with the respective ventilator via a tube elongation (Gänsegurgel 22F-22M/15, P.J. Dahlhausen &
The concentration of carbon dioxide was monitored on the side of the test lung, and was maintained between 20 and 40 mmHg. All experiments were performed under normal pressure and ambient temperature.

The **Aisys CS™** anesthesia Ventilator
The Aisys CS™ anesthesia ventilator (GE Healthcare, Chalfont St. Giles, UK) is equipped with a classical circle system, and an automatic control for end-tidal anesthetic concentration \( (F_{et}) \). Different FGFs and ascending target Fet were chosen as described below. Anesthetic consumption was documented as displayed by the Aisys CS™. The Aisys CS™ was connected with the test lung via a heat moisture exchanger (HME; DARTM, Coviden, Mansfield, MA, USA). For wash out, the target \( F_{et} \) was set to zero and the HME was left in place (Figure 1A).

The **MIRUSTM** system
The MIRUSTM™ system is a new device for administration of anesthetics via common intensive care ventilators. The device also uses anesthetic reflection instead of a circle system in order to reduce consumption of the applied anesthetic. The MIRUSTM™ device consists of a control unit (MIRUSTM™ Controller) and an interface (MIRUSTM™ Exchanger), which are inserted between a Y-piece and the patient (or test lung). Controller and Exchanger are connected by a multi-lumen cable for anesthetic administration, as well as for gas, pressure, and flow monitoring. Like Aisys CS™, the MIRUSTM™ system also controls the \( F_{et} \) automatically. The speed of wash-in can be selected in three steps, i.e., low (symbolized by a tortoise), normal (hare), and high speed (cheetah). In this study, the normal speed was selected by default. Consumption at the different target Fet was calculated via the filling level indicator of the MIRUSTM™ device. For wash-out, the target Fet was set to zero, and the MIRUSTM™ Exchanger was left in place (Figure 1B).

Figure 1: Experimental setups used in this study.
Note: (A) The circle breathing system is connected to the test lung (right side), which is equipped with two bag-valve units (BV), each with a volume of 2 L. Air (1) and oxygen (2) are connected to an anesthesia gas scavenging system (3). The Aisys CS™ (4), which consists of an electronic control mechanism and the Aladin 2 vaporization cassette, is connected to the test lung box via a heat moisture exchanger (5). (B) The MIRUSTM™ system (left), which is ventilated by a Bennett 840 ventilator with air (1) and oxygen (2), is connected to an anesthesia gas scavenging system (3). The ventilator is connected with a Y-piece to the MIRUS Controller unit and the Exchanger unit (4). The MIRUSTM™ device is connected to the test lung (right side) with two BV and 2 L volume each via a heat moisture exchanger (5). Gas samples are collected at the test lung and analyzed by a gas monitor. ICU: Intensive care unit.

Ventilation
A Puriton Bennett 840 ventilator (PB-840, Medtronics, Minneapolis, MN, USA) was used with the MIRUSTM™ system for ventilation. In case of the Aisys CS™, default ventilation of the test lung was performed with decelerating flow in volume controlled mode (SIMV-Volume Control plus) with 500 mL tidal volume, 10 breaths/min respiratory rate, 2 seconds inspiratory time, 0.5 kPa positive end-expiratory pressure, and 21% oxygen. The same ventilation settings were used for wash-out. In addition, wash-out was monitored for all experiments at high minute ventilation using the same settings as stated above, except for 1000 mL tidal volume and 20 breaths/min respiratory rate.

Experimental procedures
Three anesthetics (isoflurane, sevoflurane, and desflurane) were tested in two experimental setups (i.e., Aisys CS™ and MIRUSTM™ system (plus PB-840)) as described in Figure 1. Four different FGFs (0.5, 1.0, 2.5, and 5.0 L/min) were used with the Aisys CS™. Ascending target Fet were 0.5%, 1.0%, 1.5%, 2.0%, and 2.5% for both isoflurane and sevoflurane, and 1%, 2%, 3%, 4%, 5%, and 6% for desflurane. The increase in Fet was performed stepwise, which yielded extended wash-in times. After wash-in, the concentration was maintained for 30 minutes, and anesthetic consumption was measured as mentioned above. Projected consumption of the gas in a clinical setting was calculated using the following formula:

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\text{Projected clinical consumption of volatile anesthetics (mL/h) = consumption of model at defined concentration (mL/h) × (target } F_{et} / \text{ target concentration}) × (initial minute volume } [\text{L/min}] / 5 \text{ [L/min]}). 
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After each experimental cycle, anesthetic administration was stopped, and all times were recorded to reach 2.0%, 1.5%, 1.0%, 0.5%, and 0% isoflurane or sevoflurane, or 5.0%, 4.0%, 3.0%, 2.0%, 1.0%, and 0% desflurane, respectively. In addition, the same wash-out times were recorded with an increased minute ventilation of 20 L/min. All experimental cycles were repeated three times.

Statistical analysis
Data are expressed as mean ± standard deviation (SD) as well as mean ± standard error of the mean (SEM). 95% bias-corrected and accelerated confidence intervals in the supplementary material. Differences between the Aisys CS™ and MIRUSTM™ system regarding wash-in times (0–2.5% and 0–6%, respectively) and wash-out times (2.5–0% and 6–0%, respectively) were tested via univariate analysis of variance (ANOVA) for each anesthetic, modeling the ‘between’ factor “device” (MIRUSTM™ vs. Aisys CS™. 0.5, 1.0, 2.5, 5.0 L/min FGF). Follow-up tests were performed for significant main effects via Dunnett \( t \)-tests with the MIRUSTM™ 5 L or 20 L as a reference category. Follow-up tests for the comparison of adjacent FGF increments (0.5% vs. 1.0%, 1.0% vs. 2.5%, 2.5% vs. 5% L/min FGF) were performed with Sidak correction for multiple comparisons.

Mixed model ANOVA with the ‘between’ factor “device” (MIRUSTM™ vs. Aisys CS™. FGF 0.5, 1.0, 2.5, 5.0 L/min), and the ‘within’ factors “targeted concentration” (0.5%, 1.0%, 1.5%, 2.0%, and 2.5% for isoflurane and sevoflurane; 1%, 2%, 3%, 4%, 5%, and 6% for desflurane) were conducted.
separately for the consumption phase of each anesthetic. A univariate ANOVA was performed for significant interactions. Here, each level of the “within” factor was investigated for differences between and within MIRUS™ vs. Aisys CS™. A significant main effect “device” of the univariate ANOVA was further investigated via Sidak corrected comparison of adjacent FGF increments (0.5% vs. 1.0%, 1.0% vs. 2.5%, 2.5% vs. 5.0% L/min FGF). For each univariate ANOVA, the corrected R2 (R2c) is reported as a measure of explained variance.

Since the sample size in this study was low, statistical analyses were considered as a rough estimation of the real effect. However, the error-related variance is minimal in this model-based experimental setting. To offer the best possible estimation of the effect, statistical analyses were based on a 1000 sample-bootstrapping approach, reporting 95% bias-corrected and accelerated confidence intervals for each mean or mean difference (see supplementary information). Statistical significance was accepted at an error probability of $P \leq 0.05$.

Data analysis was performed using SPSS Statistics 24 (IBM, Armonk, NY, USA).

**Results**

**Wash-in**

The wash-in of isoflurane, sevoflurane, and desflurane decreased from 0.5 L/min to 5.0 L/min FGF; although no significant difference between adjacent FGF increments was found (isoflurane: $P > 0.999$, sevoflurane: $P \geq 0.109$, desflurane: $P \geq 0.956$; Table 1). For all testes anesthetics, wash-in was faster for the Aisys CS™ than for the MIRUS™ system ($P < 0.001$; Additional Table 1).

| System | Isoflurane (0% to 2.5%) | Sevoflurane (0% to 2.5%) | Desflurane (0% to 6.0%) |
|--------|-------------------------|--------------------------|------------------------|
| 0.5 L/min FGF | 7:38±0.16 | 10:41±0.40 | 12:31±0.45 |
| 1.0 L/min FGF | 7:34±0.32 | 8:45±0.27 | 11:39±0.16 |
| 2.5 L/min FGF | 7:00±0.05 | 8:06±0.18 | 10:53±0.42 |
| 5.0 L/min FGF | 7:02±0.08 | 7:15±0.44 | 10:01±0.08 |
| MIRUS™ MV 5L | 12:27±1.09 | 20:04±1.20 | 17:39±1.20 |

Note: Wash-in times were presented in the format hour:minute:second. Data of three independent experiments are presented as mean ± SD. Statistically insignificant (i.e., “comparable”) consumption is indicated in bold. *Sidak correction was performed for post-hoc analyses as a follow up to univariate analysis of variance (main effect “device” performed for each concentration) with MIRUSTM tested against 0.5, 1, 2.5, and 5 L/min FGF of the Aisys CS™; $\#P < 0.05$, vs. 1.0 L/min FGF; $\dagger P < 0.05$, vs. 2.5 L/min and 5.0 L/min FGF. FGF: Fresh gas flow of the Aisys CS™; MV: minute volume.

**Consumption**

The concentration of isoflurane, sevoflurane, and desflurane showed a statistically significant effect on the consumption in both Aisys CS™ and MIRUS™ system (interaction “consumption x device”: isoflurane: $F_{(4.61,65)} = 239.72, P < 0.001$; sevoflurane: $F_{(4.5,64)} = 176.3, P < 0.001$; desflurane: $F_{(5.2,143)} = 68.08, P < 0.001$; Table 2 and Additional Table 2).

Table 1: Wash-in time of isoflurane, sevoflurane, and desflurane in the Aisys CS™ fresh gas flow and the MIRUS™ system

Table 2: Consumption (mL/h) of isoflurane, sevoflurane, and desflurane related to the Aisys CS™ fresh gas flow, and the MIRUS™ system

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Similar to isoflurane, consumption of sevoflurane at 1.5% and 2.5% increased significantly from 0.5 L/min to 5.0 L/min FGF (≤ 0.05; Figure 2B and Additional Table 2), whereas consumption of isoflurane at 0.5%, 1.0%, and 2.0% increased significantly from 1.0 L/min to 5.0 L/min FGF (P ≤ 0.007). Nonetheless, consumption of the MIRUS system was higher and similar to 2.5 L/min FGF. For example, at 1%, the MIRUS system consumed an average of 10 mL/h, which is comparable to the Aisys CS system at FGF 2.5 L/min (8.4 mL/h). At higher concentrations, the consumption of the MIRUS system was between 2.5 L/min and 5.0 L/min FGF.

Consumption of desflurane 0% to 6.0% increased significantly with higher FGF (starting at 0.5 or 1.0 L/min, P ≤ 0.023; Figure 2C and Additional Table 2). The MIRUS system showed at 1% and 2% desflurane a consumption similar to 1.0 L/min FGF (P = 0.998 and P = 0.982). At 3% and 4% desflurane, the consumption of the MIRUS system was between 1.0 L/min and 2.5 L/min FGF. At the highest tested concentration of 5% and 6%, the consumption did not show a statistically significant difference FGF of 2.5 L/min (P = 0.192 and P = 0.598; Table 2), and hence were deemed as comparable.

**Wash-out**

The wash-out of isoflurane, sevoflurane, and desflurane increased from 0.5 L/min to 5.0 L/min FGF (P < 0.001; Table 3 and Additional Table 3). The MIRUS system with 5 L minute volume showed a performance between 1.0 L/min and 2.5 L/min FGF for isoflurane, and a similar performance to 1.0 L/min FGF for sevoflurane (P = 0.373) and desflurane (P > 0.999; Figure 3). By contrast, the MIRUS system with 20 L high minute volume performed similarly to 5.0 L/min FGF for all three anesthetics (P > 0.999).

**Table 3: Wash-out time of isoflurane, sevoflurane, and desflurane in the Aisys CS fresh gas flow and the MIRUS system**

| System       | Isoflurane (2.5% to 0%) | Sevoflurane (2.5% to 0%) | Desflurane (6.0% to 0%) |
|--------------|------------------------|--------------------------|-------------------------|
| 0.5 L/min    | 1:36:36±0:01:30        | 1:23:21±0:03:30          | 1:39:29±0:06:31         |
| 1.0 L/min    | 0:48:43±0:00:41        | 0:50:21±0:06:40          | 0:59:00±0:05:08         |
| 2.5 L/min    | 0:21:17±0:00:18        | 0:20:22±0:00:34          | 0:23:33±0:00:22         |
| 5.0 L/min    | 0:10:44±0:00:05        | 0:11:19±0:00:56          | 0:12:34±0:00:46         |
| 6.0%         | 0:36:18±0:02:47       | 0:55:16±0:00:16          | 0:59:46±0:03:00         |
| MV 5 L       | 0:09:38±0:00:05       | 0:12:39±0:00:30          | 0:14:15±0:00:26         |

Note: Wash-out times are presented as hour:minute:second. Data of three independent experiments are presented as mean ± SD. Univariate analysis of variance with Sidak-corrected post-hoc tests and 1000 sample bootstrapping were used for statistical comparison. P < 0.05, vs. 1.0 L/min and 2.5 L/min FGF; P < 0.05, vs. 0.5 L/min and 1.0 L/min FGF; P < 0.05, vs. 1.0 L/min FGF. FGF: Fresh gas flow of the Aisys CS system.

Figure 2: Consumption of isoflurane (A), sevoflurane (B), and desflurane (C) in the Aisys CS fresh gas flow and the MIRUS system after wash-in. Note: Each circle represents one of three independent measurements.

Figure 3: Wash-out of isoflurane (A), sevoflurane (B), and desflurane (C) in the Aisys CS fresh gas flow and the MIRUS system. Note: The dashed lines indicate the minimum alveolar concentration for each anesthetic agent. Each circle represents one out of four independent measurements.
**DISCUSSION**

This study compares the consumption and the wash-out of isoflurane, sevoflurane, and desflurane in the MIRUS™ and the Aisys CS™ systems in a laboratory model.

The Aisys CS™ showed a correlation between FGF and duration to reach the defined target concentration, which agreed with previous works. Nevertheless, a previous study that did not observe such correlation suggested an automated regulation by the Aladin™ cassette of the Aisys CS™ anesthesia ventilator.7

Comparison between Aisys CS™ and MIRUS™ system indicated a faster wash-in of the tested anesthetics in the circle breathing system. The MIRUS™ system allows three different settings of wash-in, but we assessed only one speed in this study. Of note, the stepwise increase of the target Fet resulted in extended wash-in times. A recent randomized controlled trial showed that the MIRUS™ system reached a minimum alveolar concentration (MAC) of 0.5 within two minutes for isoflurane, sevoflurane, and desflurane.12 Further increase to 1.0 MAC showed a comparable duration of approximately 2 minutes. These times are faster than the findings in this presented study. Further contradiction comes from an earlier randomized controlled study on cardiac surgery patients, which compared an AnaConDa® device with a circle breathing system and found that the device reached 0.5 MAC for 1% sevoflurane within 5 minutes.13 The differences between the results of both randomized controlled trials and our laboratory model can likely be attributed to the smaller volume of distribution. Another contributing factor is the breathing rate, which was 10 breaths per minute in our laboratory model. By contrast, the randomized controlled study did not indicate a breathing rate, but the minute ventilation was 20% higher. Since the MIRUS™ system applies a defined volume of volatile anesthetics during the inspiration phase, the MAC is restricted by the breathing rate. Depending on the selected speed, the MAC varies for each anesthetic gas. Moreover, volatile anesthetics must be delivered to the organs and the tissues after entering the bloodstream.14 The speed of distribution depends on the cardiac index, which could not be accurately modelled by the laboratory model of this study.

The consumption of isoflurane, sevoflurane, and desflurane correlated with the increase in FGF. The minute volume of the MIRUS™ system did not change during consumption; however, increasing the minute volume yields a corresponding increase in consumption. By contrast, changes and dimension of the minute volume are not relevant for circle breathing systems.15 Another notable finding is the divergent tendency of the MIRUS™ system interpolation curve for the consumption of all three gases at 3%. This divergence corresponds most likely to the spillover effect described for desflurane. Hence, the results at higher concentration might not accurately reflect the precise consumption.

**Clinical significance**

The performance of the MIRUS™ system in our study has also important ramifications for the clinical setting. Sedation with isoflurane in the intensive care unit requires 0.5 MAC (0.5%). In contrast, consumption for 0.5 MAC (1.0%) sevoflurane was relatively high with 10–15 mL/h, and was comparable to consumption for 0.5 MAC (3.0%) desflurane. Hence, the MIRUS™ reflection system demonstrated a poorer performance for sevoflurane than for isoflurane. The AnaConDa® device, however, showed a comparable consumption for both isoflurane and sevoflurane,7 which is likely due to the carbon fibers in that system. An earlier study demonstrated that integration of such carbon fibers into the MIRUS™ system improved the reflection of desflurane.5 In our study, the consumption of 3% desflurane was projected as 13 mL/h and agreed with the observed 17 mL/h in this earlier study. Similarly, projection of isoflurane consumption in our model system was 4.128 mL/h, and matched closely a recent randomized controlled trial, which found a consumption of 4.0 mL/h.16 By contrast, the consumption of sevoflurane was projected to be 11.7 mL/h, thus exceeding the consumption of 7.9 mL/h that was reported in a prospective interventional study.17

Wash-out times with MIRUS™ system corresponded to the times with the Aisys CS™ between 1.0 L/min and 2.5 L/min FGF for all three gases for a minute volume of 5 L, and 5.0 L/min FGF for a 20 L high minute volume.

The results for both Aisys CS™ and MIRUS™ system showed exponential curve progressions that were comparable to the wash-out in the clinic setting.18 In hospital, the MAC-awake is a crucial parameter for the awakening of the patient. Patients awake as soon as the concentration of the volatile anesthetic agent falls below 0.35 MAC. The corresponding wash-out time for isoflurane was more than 20 minutes, and thus the longest in our study. Hence, we recommend removing the MIRUS™ reflector, and aiming for a high minute volume. Furthermore, the wash-out should be performed at a low Fet. Removal of the reflector is an optional improvement for sevoflurane. For the less potent desflurane, the removal of the MIRUS™ reflector is irrelevant, since the MACawake falls below 2.0–2.4 within 5 minutes.12,16

**Limitations**

The results of our laboratory model might differ from human studies. We performed our experiments under ambient temperature pressure, saturated, and added volatile anesthetics and CO₂. We did not implement a body temperature pressure, saturated condition, and we did not study the influence of either ambient or body temperature pressure, as this was beyond the scope of the study. Nonetheless, we assume that these conditions likely affected CO₂ reflection, which is lower under body temperature pressure, saturated.19

As described in previous studies,19,20 we injected the volatile anesthetic agent directly into the test lung in order to avoid any interferences by administration. The concentration of the anesthetic gas was measured inside the test lung, since measurements of gas concentrations at the sampling port might have produced erroneous readings of the end-tidal concentration.21,22

All presented measurements in this study were repeated three times and showed only marginal deviation as presented in Figure 2. Maximum measurement errors of concentrations, which were measured by the gas monitor, and flow, which was measured at the ventilator, were around 5%, according to the manufacturer’s specifications. This error is expected.
to be less under the controlled laboratory conditions.

In summary, our study demonstrated that the MIRUS™ system delivers clinically relevant concentrations of anesthetic gas with satisfactory performance. Moreover, the consumption matched that of a conventional anesthesia device at a FGF between 1 L/min for isoflurane and desflurane, and 2.5 L/min for sevoflurane.

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Author contributions
Study design and data analysis: MB, DD, AM, JHN, TW; study implementation and statistical analysis: MB, DD, VV, AG; data collection: DD, VV, LP, AG; manuscript writing: MB, DD; manuscript revision: MB, DD, JHN, AM. All authors revised the manuscript and approved the final version.

Conflicts of interest
The authors declare that there is no conflict of interest.

Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Additional files
Additional Table 1: Wash-in of isoflurane (0% to 2.5%), sevoflurane (0% to 2.5%) and desflurane (0% to 6%) of the Aisys CS™ fresh gas flow compared to the MIRUS™ system.

Additional Table 2: Consumption time of isoflurane, sevoflurane and desflurane in the Aisys CS™ fresh gas flow, and the MIRUS™ system.

Additional Table 3: Wash-out time of isoflurane (2.5% to 0%), sevoflurane (2.5% to 0%) and desflurane (6% to 0%) in the Aisys CS™ fresh gas flow, and the MIRUS™ system.

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Table 1: Wash-in of isoflurane (0% to 2.5%), sevoflurane (0% to 2.5%) and desflurane (0% to 6%) of the Aisys CS™ fresh gas flow compared to the MIRUS™ system.

| System   | Mean difference (h:min) | 95% bias-corrected accelerated-confidence interval | and Statistics |
|----------|-------------------------|-------------------------------------------------|----------------|
| **Isoflurane** |                         |                                                 |                |
| MIRUS™ MV |                         |                                                 |                |
| 5L       | 0.5 L/min -4:49±0:35    | -6:10; -3:49                                   |                |
| FGF      | 1.0 L/min -4:53±0:38    | -6:16; -3:46                                   | P < 0.001      |
| FGF      | 2.5 L/min -5:26±0:35    | -6:45; -4:29                                   | P < 0.001      |
| FGF      | 5.0 L/min -5:24±0:35    | -6:43; -4:26                                   | P < 0.001      |
| **Sevoflurane** |                     |                                                 |                |
| MIRUS™ MV |                         |                                                 |                |
| 5L       | 0.5 L/min -9:22±0:40    | -10:43; -7:54                                  | P < 0.001      |
| FGF      | 1.0 L/min -11:18±0:38   | -12:30; -10:00                                 | P < 0.001      |
| FGF      | 2.5 L/min -11:58±0:38   | -13:22; -10:38                                 | P < 0.001      |
| FGF      | 5.0 L/min -12:49±0:41   | -14:07; -11:24                                 | P < 0.001      |
| **Desflurane** |                    |                                                 |                |
| MIRUS™ MV |                         |                                                 |                |
| 5L       | 0.5 L/min -5:08±0:41    | -6:33; -3:47                                   | P < 0.001      |

F_{(4,15)} = 46.24, P < 0.001, R^2 = 0.928
F_{(4,16)} = 140.29, P < 0.001, R^2 = 0.995
F_{(4,13)} = 50.19, P < 0.001, R^2 = 0.939
| Flow Rate (L/min) | FGF | Wash-in Time (min) | Wash-out Time (min) | P Value |
|------------------|-----|--------------------|--------------------|---------|
| 1.0              | FGF | -6:00±0:34         | -7:07; -4:42       | P < 0.001 |
| 2.5              | FGF | -6:46±0:40         | -8:06; -5:22       | P < 0.001 |
| 5.0              | FGF | -7:38±0:34         | -8:45; -6:25       | P < 0.001 |

Bootstrapped data are presented as mean ± SEM and 95% bias-corrected and accelerated-confidence interval. Dunnet t-test was performed as post hoc analyses with Mirus™ MV 5L as reference category. According to univariate analysis of variance with 1000 sample bootstrapping, the MIRUS™ system shows significantly higher wash-in times. FGF: Fresh gas flow of the Aisys CS™; MV: minute volume; $R^2_c$: corrected $R^2$. 
### Additional Table 2: Consumption time of isoflurane, sevoflurane and desflurane in the Aisys CS™ fresh gas flow, and the MIRUS™ system.

| System   | Consumption (h) | 95% bias-corrected confidence interval | Statistics |
|----------|-----------------|---------------------------------------|-------------|
| **Isoflurane** |                 |                                       |             |
| 0.5%     |                 |                                       |             |
| 0.5 L/min | 0.93±0.82       | 0.80-1.10                             |             |
| FGF      |                 |                                       |             |
| 1.0 L/min | 2.00±0.53       | 1.90-2.10                             | P < 0.001   |
| FGF      |                 |                                       |             |
| 2.5 L/min | 4.00±0.05       | 3.93-4.08                             | P < 0.001   |
| FGF      |                 |                                       |             |
| 5.0 L/min | 7.77±0.14       | 7.50-8.00                             | P < 0.001   |
| FGF      |                 |                                       |             |
| **MIRUS™** | 2.00±0.00       | 2.00-2.00                             |             |
| MV 5 L   |                 |                                       |             |
| **1.0%** |                 |                                       |             |
| 0.5 L/min | 1.97±0.03       | 1.90-2.00                             | P < 0.001   |
| FGF      |                 |                                       |             |
| 1.0 L/min | 3.40±0.05       | 3.30-3.50                             | P < 0.001   |
| FGF      |                 |                                       |             |
| 2.5 L/min | 8.13±0.11       | 7.90-8.30                             | P < 0.001   |
| FGF      |                 |                                       |             |
| 5.0 L/min | 15.80±0.11      | 15.60-16.00                           | P < 0.001   |
| FGF      |                 |                                       |             |
| **MIRUS™** | 4.00±0.00       | 4.00-4.00                             |             |
| MV 5 L   |                 |                                       |             |
| **1.5%** |                 |                                       |             |
| 0.5 L/min | 2.90±0.05       | 2.80-3.00                             | P < 0.001   |
| FGF      |                 |                                       |             |
| 1.0 L/min | 5.50±0.14       | 5.30-5.80                             | P < 0.001   |

*FGF* indicates fresh gas flow, *MIRUS™* indicates the MIRUS™ system.
| Volume/min | FG | Mean ± SD | Range | P value |
|------------|----|-----------|-------|---------|
| 2.5        |    | 12.10±0.55 | 12.00-12.20 | < 0.001 |
| 5.0        |    | 23.80±0.14 | 23.50-24.00 | < 0.001 |
| MIRUS™ MV 5 L |    | 8.00±0.00  | 8.00-8.00  |          |
| 2.0%       |    | 3.70±0.54  | 3.60-3.80  |          |
| FGF        |    | 7.27±0.19  | 6.90-7.60  | < 0.001  |
| 2.5        |    | 15.77±0.08 | 15.60-15.90| < 0.001  |
| 5.0        |    | 30.77±0.13 | 30.50-31.00| < 0.001  |
| MIRUS™ MV 5 L |    | 16.00±0.00 | 16.00-16.00|          |
| 2.5%       |    | 4.97±0.08  | 4.80-5.10  |          |
| FGF        |    | 8.67±0.17  | 8.30-8.90  | < 0.001  |
| 2.5        |    | 19.57±0.26 | 19.20-20.10| < 0.001  |
| 5.0        |    | 38.43±0.22 | 38.00-38.80| < 0.001  |
| MIRUS™ MV 5 L |    | 24.67±1.23 | 22.00-26.00|          |

**Sevoflurane**

| Volume/min | FG | Mean ± SD | Range | F(4,10) | P value | R² |
|------------|----|-----------|-------|---------|---------|----|
| 0.5%       |    | 1.00±0.00 | 1.00-1.00 | 70.04   | < 0.001 | 0.952 |
| Flow Rate (L/min) | FGF (mg/L) | Range (mg/L) | P-value |
|------------------|------------|--------------|---------|
| 1.0              | 2.00±0.00  | 2.00-2.00    | 0.484   |
| 2.5              | 4.33±0.13  | 4.10-4.60    | 0.007   |
| 5.0              | 8.33±0.30  | 8.00-9.00    | <0.001  |
| MIRUS™           | 4.67±0.62  | 4.00-6.00    |         |
| MV 5 L           |            |              |         |
| 1.0%             |            |              |         |
| 0.5 L/min        | 2.33±0.32  | 2.00-3.00    |         |
|                  |            |              |         |
| 1.0 L/min        | 4.00±0.00  | 4.00-4.00    | 0.432   |
| 2.5 L/min        | 8.37±0.16  | 8.20-8.70    | 0.002   |
| 5.0 L/min        | 16.00±0.00 | 16.00-16.00  | <0.001  |
| MIRUS™           | 10.00±1.08 | 8.67-11.50   |         |
| MV 5 L           |            |              |         |
| 1.5%             |            |              |         |
| 0.5 L/min        | 3.00±0.00  | 3.00-3.00    |         |
|                  |            |              |         |
| 1.0 L/min        | 5.33±0.31  | 5.00-6.00    | 0.013   |
| 2.5 L/min        | 12.47±0.16 | 12.20-12.80  | <0.001  |
| 5.0 L/min        | 24.33±0.31 | 24.00-25.00  | <0.001  |
| MIRUS™           | 14.67±0.62 | 14.00-16.00  |         |
| MV 5 L           |            |              |         |
| 2.0%             |            |              |         |
| 0.5 L/min        | 4.33±0.30  | 4.00-5.00    |         |

F(4,10) = 98.62, \( P < 0.001 \), \( R^2_c = 0.965 \)

F(4,10) = 510.33, \( P < 0.001 \), \( R^2_c > 0.993 \)

F(4,10) = 190.81, \( p < 0.001 \),
|                | Flow Rate (L/min) | FGF       | p Value | R² Value |
|----------------|-------------------|-----------|---------|----------|
| 1.0 L/min FGF  | 8.00 ± 0.00       | 8.00-8.00 | 0.100*  | > 0.982  |
| 2.5 L/min FGF  | 16.43 ± 0.24      | 16.00-16.90 | 0.001   |          |
| 5.0 L/min FGF  | 32.67 ± 0.32      | 32.00-33.00 | 0.001   |          |
| MIRUS™ MV 5 L  | 22.67 ± 1.62      | 20.00-26.00 |        |          |
| 2.5%            |                   |           |         |          |
| 0.5 L/min FGF  | 5.33 ± 0.32       | 5.00-6.00 | 0.001   | 0.998    |
| 1.0 L/min FGF  | 9.33 ± 0.32       | 9.00-10.00 | 0.001   |          |
| 2.5 L/min FGF  | 20.37 ± 0.17      | 20.10-20.70 | 0.001  |          |
| 5.0 L/min FGF  | 42.00 ± 0.00      | 42.00-42.00 | 0.001  |          |
| MIRUS™ MV 5 L  | 30.67 ± 0.62      | 30.00-32.00 |        |          |
| Desflurane 1.0%|                   |           |         |          |
| 0.5 L/min FGF  | 1.57 ± 0.06       | 1.50-1.63 | 0.877   | 0.916    |
| 1.0 L/min FGF  | 3.20 ± 0.14       | 3.00-3.50 | 0.016   |          |
| 2.5 L/min FGF  | 8.03 ± 0.11       | 7.80-8.20 | 0.001   |          |
| 5.0 L/min FGF  | 14.83 ± 0.08      | 14.7-15.00 | 0.001  |          |
| MIRUS™ MV 5L   | 4.13 ± 1.33       | 2.17-7.00 |        |          |
| Percentage | Flow Rate (L/min) | FGF | p | FGF | p | FGF | p | FGF | p |
|------------|------------------|-----|---|-----|---|-----|---|-----|---|
| 2.0%       | 0.5              | 3.4±0.29 | 3.00-4.00 | $F_{(4,11)} = 681.278$, $P < 0.001$, $R^2 = 0.995$ |
|            | 1.0              | 6.33±0.30 | 6.00-7.00 | $P = 0.003$ |
|            | 2.5              | 15.07±0.29 | 14.50-15.60 | $P < 0.001$ |
|            | 5.0              | 29.07±0.21 | 28.70-29.50 | $P < 0.001$ |
|            | MIRUS™           | 6.88±0.50 | 6.00-8.00 | |
| 3.0%       | 0.5              | 5.00±0.00 | 5.00-5.00 | $F_{(4,11)} = 853.355$, $P < 0.001$, $R^2 = 0.995$ |
|            | 1.0              | 9.67±0.31 | 9.00-10.00 | $P = 0.001^*$ |
|            | 2.5              | 22.80±0.55 | 21.70-23.80 | $P < 0.001$ |
|            | 5.0              | 43.00±0.53 | 42.00-44.00 | $P < 0.001$ |
|            | MIRUS™           | 13.00±0.55 | 12.00-14.00 | |
| 4.0%       | 0.5              | 6.17±0.15 | 6.00-6.50 | $F_{(4,11)} = 908.994$, $P < 0.001$, $R^2 = 0.987$ |
|            | 1.0              | 11.33±0.30 | 11.00-12.00 | $P = 0.002$ |
|            | 2.5              | 30.27±0.39 | 29.80-31.10 | $P < 0.001$ |
|            | 5.0              | 57.00±0.52 | 56.36-57.60 | $P < 0.001$ |
|            | MIRUS™           | 21.25±0.96 | 20.00-24.00 | |
| MV 5 L | 5.0%       |
|--------|------------|
| 0.5 L/min | 8.50±0.72 | 7.50-10.00 | $F_{(4,11)} = 186.508, \ p < 0.001, R_c^2 = 0.980$ |
| FGF    |            |
| 1.0 L/min | 15.50±0.27 | 15.08-15.90 | $P = 0.177$ |
| FGF    |            |
| 2.5 L/min | 37.43±0.32 | 36.80-38.00 | $P < 0.001$ |
| FGF    |            |
| 5.0 L/min | 71.83±0.67 | 70.50-73.00 | $P < 0.001$ |
| FGF    |            |
| MIRUS™ | 31.00±2.80 | 25.52-38.00 |            |

| MV 5 L | 6.0%       |
|--------|------------|
| 0.5 L/min | 10.83±1.00 | 9.50-13.00 | $F_{(4,14)} = 306.655, \ P < 0.001, R_c^2 = 0.985$ |
| FGF    |            |
| 1.0 L/min | 19.04±0.49 | 18.00-20.27 | $P = 0.023$ |
| FGF    |            |
| 2.5 L/min | 44.77±0.19 | 44.40-45.10 | $P < 0.001$ |
| FGF    |            |
| 5.0 L/min | 86.50±0.72 | 85.00-87.50 | $P < 0.001$ |
| FGF    |            |
| MIRUS™ | 40.70±2.38 | 34.41-45.09 |            |

Bootstrapped data are presented as mean ± SEM and 95% bias-corrected and accelerated-confidence interval. Sidak correction was performed for post hoc analyses as a follow up to univariate analysis of variance (main effect “device” for isoflurane, with adjacent FGFs tested against each other (0.5 vs. 1 L/min FGF; 1 vs. 2.5 L/min FGF, 2.5 vs. 5 L/min FGF). FGF: Fresh gas flow of the Aisys CS™; MV: minute volume; $R_c^2$: corrected $R^2$. 
Table 3: Wash-out time of isoflurane (2.5% to 0%), sevoflurane (2.5% to 0%) and desflurane (6% to 0%) in the Aisys CS™ fresh gas flow, and the MIRUS™ system.

| System               | Wash-out time 95% bias-corrected and accelerated-confidence interval | Statistics |
|----------------------|---------------------------------------------------------------|-------------|
| **Isoflurane (2.5% to 0%)** |                                                               |             |
| 0.5 L/min FGF        | 1:36:36±0:01:3 1:33:40-1:39:27                                |             |
| 1.0 L/min FGF        | 0:48:43±0:00:4 0:47:17-0:49:38                                 | P < 0.001* |
| 2.5 L/min FGF        | 0:21:17±0:00:1 0:20:38-0:21:43                                 | P < 0.001* |
| 5.0 L/min FGF        | 0:10:44±0:00:0 0:10:33-0:10:51                                 | P < 0.001* |
| MIRUS™ MV 5 L        | 0:36:18±0:02:4 0:33:18-0:42:12                                 |             |
| MIRUS™ MV 20 L       | 0:09:38±0:00:0 0:09:26-0:09:48                                 |             |
| **Sevoflurane (2.5% to 0%)** |                                                               |             |
| 0.5 L/min FGF        | 1:23:21±0:01:5 1:20:00-1:27:00                                 |             |
| 1.0 L/min FGF        | 0:50:21±0:03:3 0:46:01-0:58:02                                 | P < 0.001**|
| 2.5 L/min FGF        | 0:20:22±0:00:1 0:20:02-0:21:02                                 | P < 0.001**|
| 5.0 L/min FGF        | 0:11:19±0:00:2 0:10:05-0:12:03                                 | P = 0.003**|
| MIRUS™ MV 5 L        | 0:55:16±0:00:0 0:54:58-0:55:29                                 |             |
| MIRUS™ MV 20 L       | 0:12:39±0:00:1 0:12:18-0:12:58                                 |             |
| **Desflurane (6% to 0%)** |                                                               |             |
| FGF               | Mean ± SEM  | 95% Bias-Corrected and Accelerated Confidence Interval | P  |
|-------------------|-------------|-------------------------------------------------------|-----|
| 0.5 L/min FGF     | 1:39:29±0:03:1 | 1:33:47-1:45:47                                       | < 0.001*** |
| 1.0 L/min FGF     | 0:59:00±0:02:2 | 0:54:31-1:04:07                                       | < 0.001*** |
| 2.5 L/min FGF     | 0:23:33±0:00:1 | 0:23:07-0:23:49                                       | < 0.001*** |
| 5.0 L/min FGF     | 0:12:34±0:00:2 | 0:12:01-0:13:27                                       | = 0.016*** |
| MIRUS™ MV 5 L     | 0:59:46±0:01:3 | 0:56:18-1:01:42                                       |                |
| MIRUS™ MV 20 L    | 0:14:15±0:00:1 | 0:13:56-0:14:34                                       |                |

Wash-out times were presented in the format hour:minute:second. Bootstrapped data are presented as mean±SEM and 95% bias-corrected and accelerated-confidence interval. *Sidak correction was performed for post-hoc analysis as follow-up to univariate analysis of variance ($F_{(5,18)} = 959.04$, $P < 0.001$, $R^2_c = 0.996$). **Sidak correction was performed for post-hoc analysis as follow-up to univariate ANOVA ($F_{(5,18)} = 474.30$ $P < 0.001$, $R^2_c = 0.992$). ***Sidak correction was performed for post-hoc analysis as follow-up to univariate ANOVA ($F_{(5,17)} = 351.02$, $p < 0.001$, $Rc^2 = 0.990$). All Sidak correction was with adjacent FGFs tested against each other (0.5 vs. 1 L/min FGF; 1 vs. 2.5 L/min FGF; 2.5 vs. 5 L/min FGF). FGF: Fresh gas flow of the Aisys CS™; MV: minute volume; $R^2_c$: corrected $R^2$. 