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Original Article

A novel device for target controlled administration and reflection of desflurane – the Mirus™

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Summary

The Anaconda™ system is used to deliver inhalational sedation in the intensive care unit in mainland Europe. The new Mirus™ system also uses a reflector like the Anaconda; however, it also identifies end-tidal concentrations from the gas flow, injects anaesthetics during early inspiration, controls anaesthetic concentrations automatically, and can be used with desflurane, which is not possible using the Anaconda. We tested the Mirus with desflurane in the laboratory. Compared with an external gas monitor, the bias (two standard deviations) of the end-tidal concentration was 0.11 (0.29)% volume. In addition, automatic control was reasonable and maximum concentration delivered was 10.2%, which was deemed to be sufficient for clinical use. Efficiency was > 80% and was also deemed to be acceptable, but only when delivering a low concentration of desflurane (≤ 1.8%). By modifying the reflector, we improved efficiency up to a concentration of 3.6%. The Mirus appears to be a promising new device for long-term sedation with desflurane on the intensive care unit, but efficiency must be improved before routine clinical use becomes affordable.

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Introduction

Since the first clinical trial looking at sedation with inhalational anaesthetic agents in the intensive care unit (ICU) [1], a number of studies have shown better control of sedation compared with intravenous drugs [2]. However, inhalational sedation has only become more popular with the advent of the Anaconda™ system (Sedana Medical, Uppsala, Sweden) [3]. Instead of a circle system, the Anaconda (Fig. 1a) uses a specific anaesthetic reflector to reduce anaesthetic agent wastage. This reflector, inserted between the Y-piece of the breathing circuit and the patient (Fig. 1b), is similar to a heat and moisture exchanger, takes up 90% of exhaled anaesthetic, and resupplies this during the next inspired breath delivered by the mechanical ventilator. A syringe pump delivers liquid isoflurane or sevoflurane into a porous hollow rod called an evaporator. The technical performance and reflection characteristics of the Anaconda have been described in a previous study [4]. The Anaconda can be used with common ICU ventilators, and carbon dioxide absorbers and circle systems are not required.

The American guidelines regarding sedation of critically ill patients do not mention inhalational anaesthetics [5]. However, inhalational sedation has become more and more popular in mainland Europe,

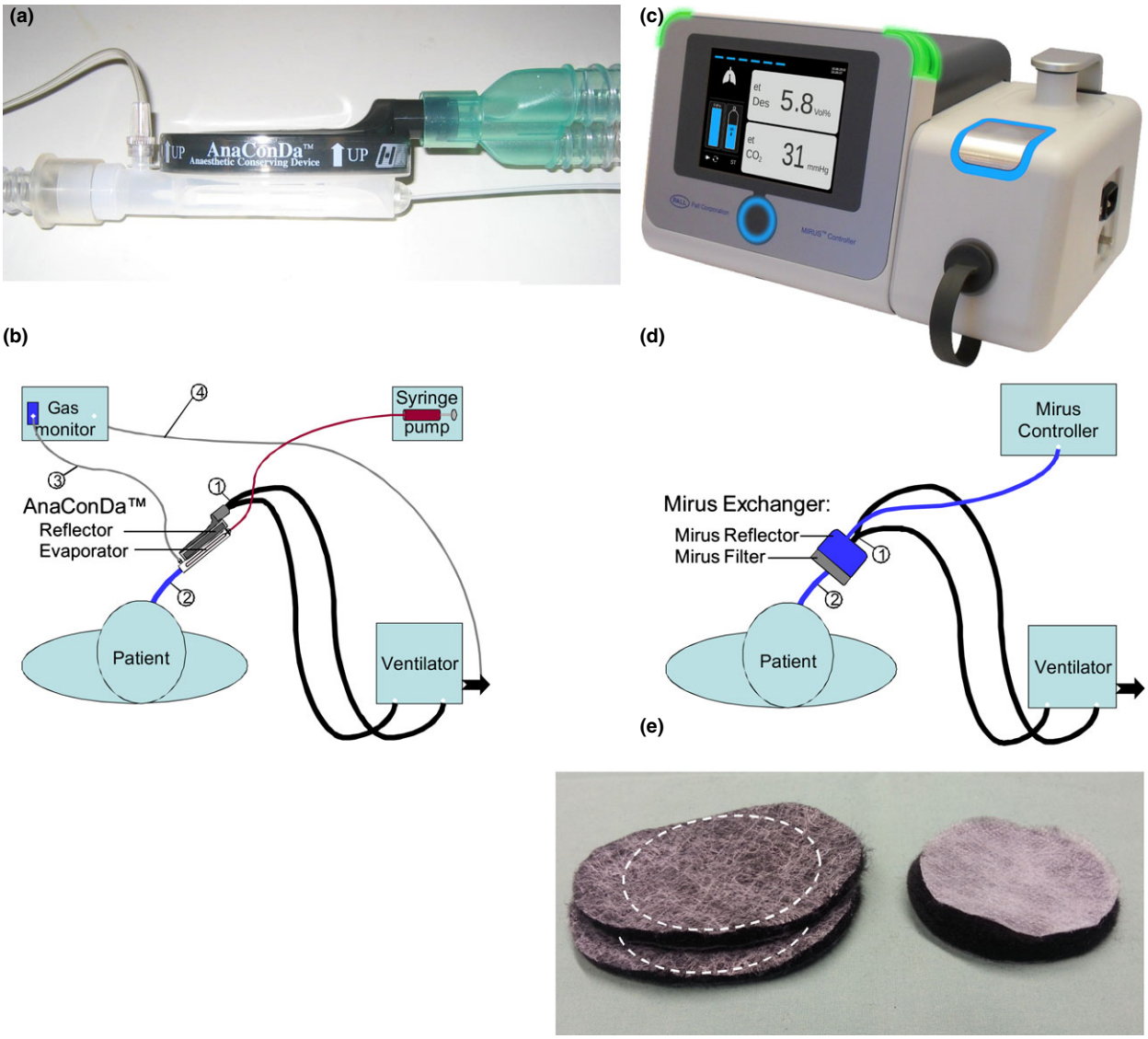

Figure 1 (a) Anaconda device. (b) Set-up of the Anaconda: the Anaconda is inserted between the Y-piece (1) and the tracheal tube (2). Liquid isoflurane or sevoflurane is administered by a syringe pump into a hollow rod (Evaporator). An external gas monitor must be used (3 = sample gas line). Active and passive scavenging systems are available and should be connected to the gas outlet of the ventilator (black arrow). Sample gas should also be scavenged (4 = sample gas scavenging line). (c) Mirus device. (d) Set-up of the Mirus system: the interface (Mirus Exchanger) is inserted between the Y-piece (1) and the tracheal tube (2). The interface is connected with the control unit by a multilumen cable (blue line). An active anaesthesia gas scavenging system (black arrow), connected to the vacuum system, is provided by the manufacturer. (e) Volatile anaesthetic reflector of the Anaconda (two layers, left side) and of the Mirus (right side). In our second experiment, the Mirus reflector was replaced by a two-layered cut-out of the Anaconda reflector (dashed lines).

with over 30 000 single-use Anaconda systems sold in Germany alone in 2013. The German sedation guidelines [6] recommend inhalational sedation in patients whose lungs are mechanically ventilated as an alternative to intravenous sedation, especially if rapid awakening, recovery of cognitive functions or mobilisation is desired.

Because of its more favourable kinetics [7, 8], and higher stability compared with sevoflurane [9, 10], desflurane may be ideally suited for sedation in ICU;

however, it cannot be delivered by the Anaconda. This is because of the low boiling point of desflurane, meaning it cannot be administered using a syringe pump, as is required by the design of the Anaconda.

A new device has recently been developed called the Mirus™ (Pall Medical, Dreieich, Germany), and it is the first to administer desflurane using reflection (Fig. 1c), instead of a circle system. The Mirus system can also be used for the delivery of sevoflurane and isoflurane. Unlike the Anaconda, the Mirus delivers anaesthetic and monitors gas concentrations as well as ventilation parameters on its own (Fig. 1d). It also offers automatic target control of the end-tidal anaesthetic concentration.

We decided to evaluate the Mirus in a bench study, and measured accuracy and precision of the measurements it made, the anaesthetic vapour injection, the automatic control of the end-tidal concentrations, the highest achievable concentration, and anaesthetic consumption at different target concentrations. To test the hypothesis that efficiency could be improved and wastage reduced, we tested the Mirus system after replacing its anaesthetic reflector with that of the Anaconda.

Methods

The Mirus consists of a control unit, with an anaesthetic-specific reservoir, connected to an interface with an internal volume of 100 ml by a multilumen cable (Fig. 1d). The interface, inserted between the Y-piece and the tracheal tube, consists of a reflector and a filter. The reflector also contains cables for gas injection and for measuring gas pressure, flow and concentration. The filter acts as a heat and moisture exchanger as well as a bacteria, virus and particle filter. Airway pressure and respiratory flow are continuously measured and displayed. Sample gas is aspirated at a flow rate of 200 $ml.min^{-1}$ and re-fed into the interface. Administration of the anaesthetic vapour occurs by pulsatile injection at the expected start of inspiration, which is extrapolated from the preceding respiratory cycles. Anaesthetic vapour is injected into gas circulating at a high rate of 400 $ml.min^{-1}$ between the interface and the control unit, to dilute and quickly transport the injected vapour to the patient. The end-tidal concentration is controlled automatically to a set target value. The speed of control can be altered to adjust the rate of wash-in of the agent.

We chose to test the Mirus using desflurane only, as this is a new option for inhalational sedation, and chose the moderate control speed throughout the test. The Mirus system, a non-rebreathing ventilator (Evita 4; Dräger Medical, Lübeck, Germany), a carbon dioxide source and a gas monitor (Vamos; Dräger Medical) were connected to a test lung (3-L-Chloroprene breathing bag, accessory for Zeus™; Dräger Medical), as shown in Fig. 2. The Mirus control unit was placed on a precision balance (TC20K; G&G GMBH, Neuss, Germany). Data from the balance and the gas monitor, which recorded desflurane and carbon dioxide concentrations every 100 ms, were stored online on a personal computer. The end-tidal desflurane concentration as displayed by the Mirus was recorded manually after each breath.

Mechanical ventilation parameters were set as follows: inspired oxygen concentration 21%; positive end-expiratory pressure 3 kPa; tidal volume 500 ml; frequency 10 bpm; inspiratory to expiratory ratio 1:1; and inspiratory flow 60 $l.min^{-1}$. In the Mirus control unit, the target concentration was set to 0.1 minimum alveolar concentration (MAC) (0.6% volume), then

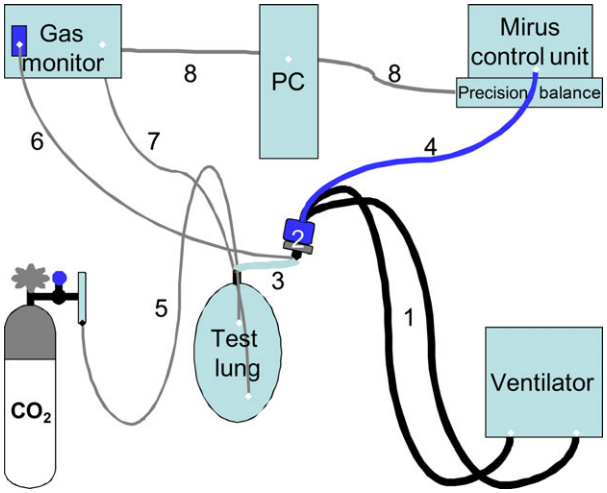

Figure 2 Experimental set-up of bench study. The Mirus control unit for desflurane, a ventilator, a carbon dioxide source and a gas monitor are connected to a test lung as shown. The control unit is positioned on a precision balance. Data from balance and gas monitor are stored online on a personal computer (PC): (1) ventilatory tubing; (2) Mirus interface; (3) bronchoscopy port; (4) Mirus interface cable; (5) carbon dioxide line; (6) sample gas line; (7) sample gas refeeding line and (8) serial communication cable.

increased every 5 min by 0.1 MAC up to 1.8 MAC (10.8%), and then decreased by 0.1 MAC down to zero. We selected this protocol so that we could test the Mirus system to its limits.

We then modified the Mirus reflector by replacing the carbon disc with a two-layered cut-out of the reflector of the Anaconda, and repeated the testing protocol. This was done to test whether the consumption of desflurane could be further decreased by altering the type of reflector used.

With regards to calculation of efficiency, consumption of anaesthetic gases depends on the concentration used, patient factors (uptake), and the anaesthetic device itself. With a reflection system such as the Mirus, the main factors determining consumption are the minute volume and the characteristics of the reflector. In physics, efficiency is a dimensionless measure used to describe processes of energy conversion. Efficiency is commonly expressed as proportion, 100% meaning that all the energy put into a system (E_{input}) is converted to the desired form of energy (E_{output}):

$$\text{Efficiency} = \frac{E_{output}}{E_{input}}$$

In the case of a reflector, we deal with vapour volume. First, we have the volume of vapour used by the system (V_{used}). Ideally, we would relate this volume to the volume taken up by the patient (V_{uptake}). Efficiency would then be:

$$\text{Efficiency} = \frac{V_{uptake}}{V_{used}}$$

However, uptake is difficult to assess, as it depends on patient characteristics such as volume of distribution and perfusion, exposure time, evaporation through skin or open wounds, unavoidable leakage such as tracheal tube suctioning, and – in the case of sevoflurane – metabolism by the patient. It can only be measured in a totally closed system, which is not in routine clinical use. We therefore related V_{used} to the vapour volume that would be used in an open system (V_{open} = minute volume × concentration). Obviously, V_{open} will be higher than V_{used}, hence:

$$\text{Efficiency} = 1 - \frac{V_{used}}{V_{open}}$$

By defining efficiency like this, we also arrive at a dimensionless figure. Translated into words, one could say 'the proportion of vapour saved compared to an open system'. Expressed as a percentage, efficiency may vary from 0% (no savings at all compared with an open system) with almost 100% (maximum savings compared with an open system). Defined this way, efficiency cannot exceed 100%.

Therefore, efficiency was calculated as follows:

$$\text{Efficiency } (\%) = 100 - 100 \times \frac{V_{liquid} \times F_{BTPS}}{\sum_{i=1}^{i=n} MV_i \times t_i \times C_i/100}$$

where V_{liquid} (ml) is the consumed volume of liquid desflurane; F_{BTPS} (l.ml) is the factor for calculating vapour volume from liquid volume under body temperature pressure-saturated conditions (F = 0.2373 for desflurane) [11]; MV_i ($l.min^{-1}$) is the minute ventilation volume during time interval i; t_i (min) is the length of time interval i; and C_i (% volume) is the end-tidal anaesthetic concentration during time interval i.

If values appeared to be normally distributed (using the Kolmogorov–Smirnov test), data were presented as mean (SD). Data analysis was performed using Excel 2007 (Microsoft Corporation, Redmond, WA, USA). The stored high-resolution tracings of the gas monitor were analysed by an observer blinded to the Mirus readings. End-tidal desflurane concentrations of all 1800 single breaths were determined by averaging each expiratory plateau (Fig. 3a). These values were compared with the end-tidal concentrations displayed by the Mirus applying the method proposed by Bland and Altman [12]. Peak and mean inspired concentrations during all desflurane injections were also determined from the high-resolution tracings, divided by the preceding end-tidal concentration and expressed as proportion.

To evaluate automatic control, the swing of the end-tidal gas measurements around the target was plotted over time (Fig. 3b,c). The end-tidal concentrations, when desflurane injection was stopped or re-started, were divided by the respective target concentration and expressed as a proportion. Consumption of desflurane was calculated by dividing the weight loss of the control unit (including the desflurane reservoir) by the specific weight of desflurane ($1.465\ g.ml^{-1}$). Consumption of the increasing and decreasing series for each target was averaged and extrapolated to the hour. This was repeated for the second experiment with the modified Mirus reflector.

Results

End-tidal desflurane concentrations displayed by the Mirus agreed with those extracted from the high resolution recordings of the gas monitor with high accuracy, with a bias of 0.11, and precision (two standard deviations of measurement error) 0.29% volume (Fig. 4). At high concentrations, there was slight overestimation by the Mirus. Desflurane vapour injection could be detected as a peak concentration during the inspiratory flow phase of some breaths (Fig. 3a–c). Peak and mean concentrations during the inspiratory flow phase were mean (SD) 173% (22%) or 134% (12%), respectively, of the preceding end-tidal concentration (Fig. 3a). At lower target concentrations, desflurane injections occurred during fewer consecutive breaths. The number of these breaths increased with higher target concentrations. At the highest target, desflurane was injected during every breath.

Figure 3c shows the swing of the end-tidal concentration around the target. Desflurane injections restarted when the end-tidal concentration had dropped to a mean (SD) of 81% (4%) of the target, and stopped when 117% (9%) of the target was reached (Fig. 3b). The mean (SD) time interval between the two restarts was 2.6 (0.8) min.

The highest end-tidal concentration of desflurane achieved was 10.2%. With the modified reflector, using the same settings, the highest value achieved was 10.8%, which was our target.

Consumption of desflurane with the standard Mirus reflector and the modified reflector is shown in Fig. 5. For both, the increase in consumption was disproportionately higher as the target concentration was increased. Over the whole experiment, efficiency was 42% for the standard reflector and 64% for the modified reflector.

Efficiency was higher than 80% for the first three targeted values with the standard reflector (up to 1.8% desflurane), and for the first six targeted values using the modified reflector (up to 3.6% desflurane).

Discussion

In this bench study, we found the Mirus to be a useful and reliable system for administration of desflurane with a common intensive care ventilator. Determination of the end-tidal anaesthetic concentration was appropriate, timely injection of anaesthetic vapour was excellent, and automatic control of the end-tidal concentration was clinically acceptable despite a 20% swing around the set target. However, efficiency needs to be improved to lower the consumption of desflurane. In this study, we have shown that this can be achieved by selecting other materials for the anaesthetic reflector inside the Mirus.

Like the Anaconda, the new Mirus system also uses a reflector to reduce wastage. However, the Mirus has its own control unit for determination of the end-tidal concentration and for target-controlled administration of the anaesthetic agent. Therefore, other devices such as an external gas monitor or a syringe pump are not needed. In addition, it can be used to administer desflurane, which is not possible using the Anaconda because the low boiling point of desflurane prohibits delivery via a syringe pump.

To verify the end-tidal concentrations displayed by the Mirus, we used an additional gas monitor. Gas was sampled between the Mirus interface and the tracheal tube. Bias and random measurement error were small, indicating good agreement of both readings. Accurate determination of the actual value is obviously a precondition for automatic control of a set value.

With any reflection system, determination of the end-tidal anaesthetic concentration may be challenging. Gas monitors used with the Anaconda display falsely high readings as end-tidal concentrations. The inspiratory concentrations shown are always lower than the end-tidal ones, even during the initial washin, which obviously cannot be true. This phenomenon has been described before [13]. In brief, for assignment of the concentration measurements to the phases of the respiratory cycle, common gas monitors rely on the carbon dioxide signal. At the end of expiration, 100 ml of dead space within the Anaconda, which is situated between the Y-piece and the patient, will contain exhaled carbon dioxide. At the same time, a cloud of anaesthetic vapour builds up as the syringe pump continues to deliver anaesthetic. With the next inspiration, this cloud will pass the gas sampling port together with carbon dioxide-rich air and the gas monitor will erroneously display this early inspiratory peak as end-tidal, and thereby give a falsely high reading.

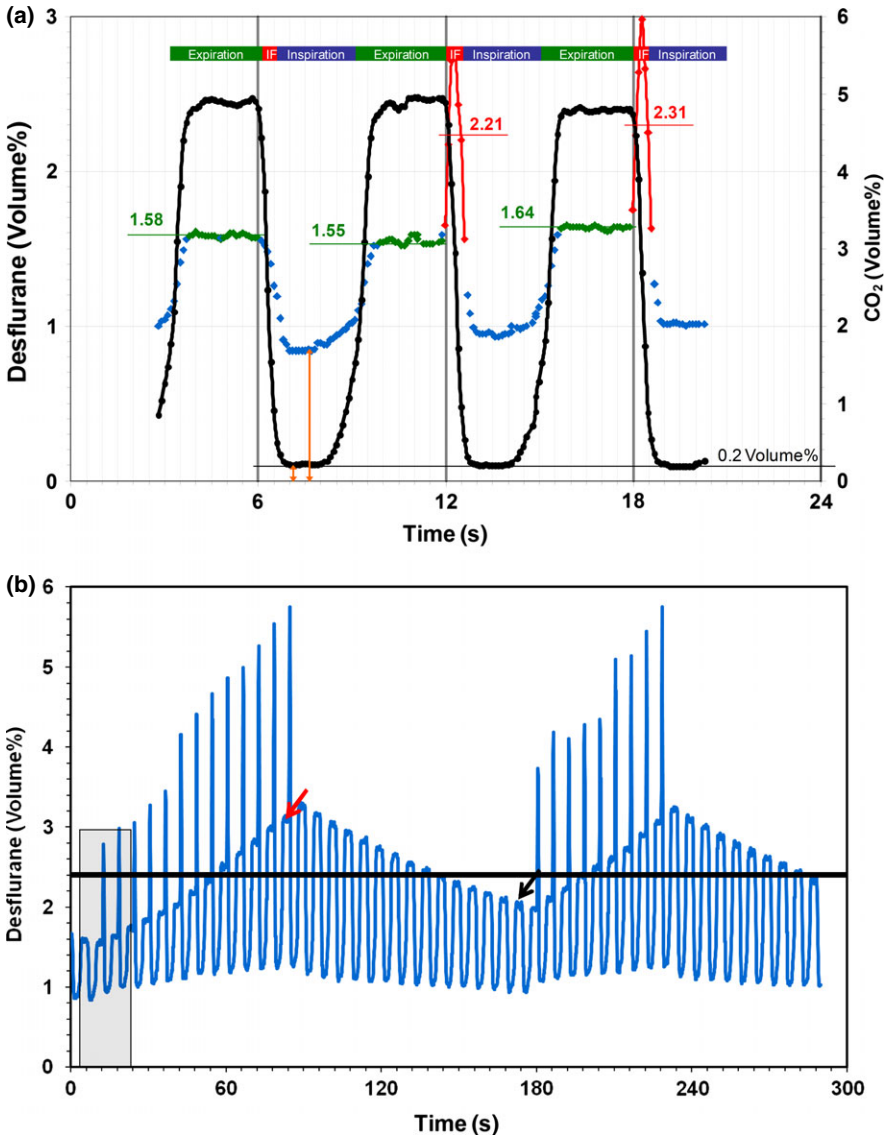

Figure 3 (a) High-resolution recording (every 100 ms) of the concentration of desflurane (left axis, blue-green-red line and dots) and carbon dioxide (CO_2, right axis, black line) during three breaths, recorded by the Vamos gas monitor. During the beginning of the inspiratory flow phase (IF), CO_2 is still high because the first 100 ml of gas from the Mirus interface is passing the gas sampling port. Thereafter, the CO_2 trace decreases not down to zero, but to 0.2% (small orange arrow) indicating minor CO_2 reflection by the Mirus reflector. The desflurane trace clearly shows the expiratory plateau. By averaging each plateau (green lines), end-tidal concentration of all 1800 single breaths were determined. During the first inspired breath, the concentration decreases to about 50% (large orange arrow), indicating desflurane reflection. After the last two expirations, there is a high peak of the desflurane concentration during the inspiratory flow phase, which lasts only 0.5 s (red lines: mean concentration during this peak). Thereafter, the desflurane concentration drops to similar values as during the previous expiration, indicating the end of desflurane injection. (b) High-resolution recording (every 100 ms) of the desflurane concentration recorded by the Vamos gas monitor over 5 min, with a target concentration of 2.4% (black line) including the three breaths from Fig. 3a (shaded area). From the second breath onwards, 13 breaths with peaks during the initial inspiratory flow phase indicating desflurane vapour injection can be seen. At an end-tidal concentration of 3.11% (red arrow), the last injection is applied. Thereafter, the concentration decreases down to 2.02% (black arrow), after which desflurane is once more injected during the following nine breaths.

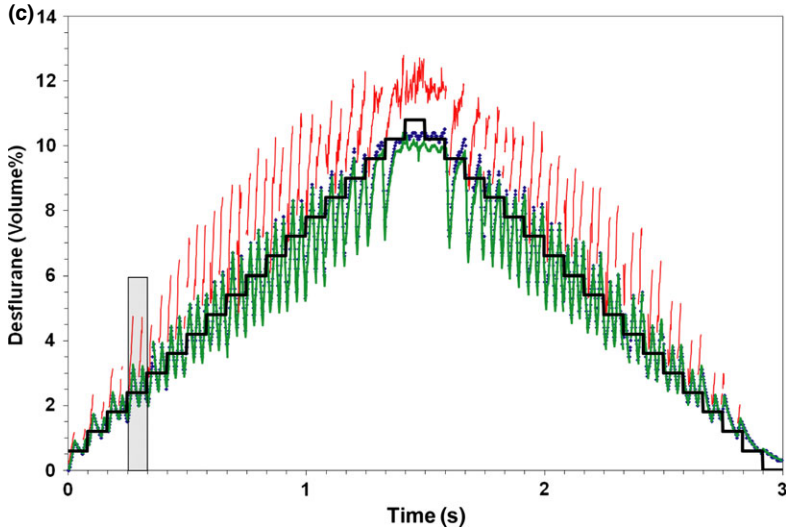

Figure 3 (c) Concentration of desflurane over the 3 h of the first bench study. The shaded area corresponds to data from Fig. 3b. The target concentration (black line) was increased stepwise every 5 min by 0.6% up to a maximum of 10.8%, and then down again. The end-tidal concentrations recorded by the gas monitor (green line) are swinging around the target. Those recorded by the Mirus itself (blue spots) are overlapping except with the very high values in the middle of the experiment. Red lines show the mean inspiratory concentrations while desflurane was injected (cf. Fig. 3a). When a low target is set, injection of desflurane occurs during only a certain number of breaths, but when a high target is set, desflurane is constantly injected with every single breath.

In contrast, assignment of the concentration measurements with the Mirus does not rely on carbon dioxide but on the flow. This is possible because the control unit of the Mirus also measures respiratory pressures and flow. Obviously, this must take into account the time lag associated with side-stream gas measurements. To our knowledge, the Mirus is the only commercially available monitor assigning concentrations to the phases of the respiratory cycle according to flow.

We then evaluated delivery of the anaesthetic. The principle of reflection calls for alternative modes of anaesthetic delivery, which must take place between the reflector and the patient into air moving back and forth. To be efficient, the anaesthetic should be delivered at the beginning of inspiration, to be carried as far as possible into the lungs. In spontaneously breathing patients, flow at the beginning of inspiration is typically high. This peak in flow must not be missed, otherwise the anaesthetic agent would remain in the tracheal tube and upper airways, and be exhaled again with the next expired breath. In our bench study, we chose a short inspiratory flow time of only 0.5 s. Figure 3a shows how well this short phase is taken advantage of. However, we did not use other ventilation modes with decelerating flows nor simulate irregular respiratory cycles as can be seen with spontaneous breathing in some patients.

Mean inspiratory concentrations during desflurane injections were only 134% of the preceding end-tidal concentration (Fig. 3a). This is unlikely to elicit sympathetic activation as described in the literature [14, 15]. However, we only evaluated moderate control speed in this study, and the higher setting needs separate evaluation.

We describe the automatic control algorithm as follows: at 80% of target, a series of vapour injections during consecutive inspired breaths starts and continues until 120% of target is reached. With higher targets, more desflurane is injected during one breath, more repetitive injections are needed to reach 120% of target and the resultant pause is shortened as the concentration falls faster. Thus, the time interval between two starts is relatively constant at 2.6 min in our bench study.

A swing of 20% around the target may be criticised. However, with irregular spontaneous breathing and incomplete exhalation, end-tidal concentrations

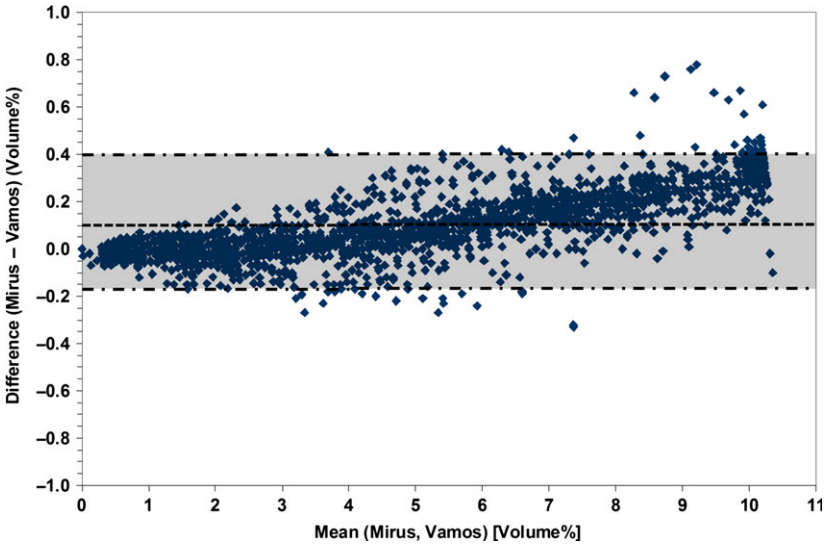

Figure 4 Bland–Altman diagram for comparison of the end-tidal concentrations measured by the gas monitor and those displayed by the Mirus. The difference between the measurements for each single breath is plotted against the mean of the two measurements. With high concentrations, there is a small overestimation by the Mirus, however, bias (0.11%, dashed line) and random measurement disagreement (0.29%, shaded area) are small and not clinically relevant.

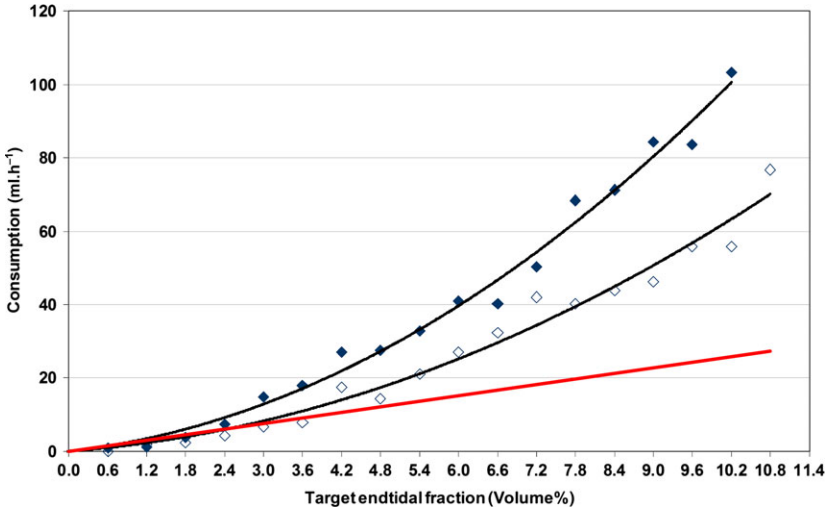

Figure 5 Consumption of desflurane over the range of the target concentration set using the Mirus with the standard reflector (filled diamonds) and using the modified Mirus reflector (unfilled diamonds). The increase in consumption is disproportionately high with increasing concentrations, indicating a decrease in efficiency. The red line indicates an efficiency of 80%.

may be erroneously detected as too low; automatic dosing could subsequently lead to anaesthetic overdose. On the other hand, when the concentration is truly below the target, it will not rise substantially with one or a few injections. Given the short time interval between concentration peaks, which is not enough to reach equilibration, we assume that the oscillations measured in expired air will be attenuated in the brain tissue. Also, in clinical practice, we did not see clinical signs of an alternating sedation level nor oscillations in bispectral index (own unpublished observations).

The highest concentration achieved was 10.2% desflurane, corresponding to 1.7 MAC in a 60-year-old patient [16]. With the use of a more efficient reflector, higher

concentrations could be reached. However, the dose used for ICU sedation is commonly 0.3–0.5 MAC [3, 17].

Efficient application of inhaled anaesthetics can be achieved by rebreathing all gases after carbon dioxide removal or by specific reflection of the anaesthetic [18, 19]. Anaesthetic reflection carries the potential advantage that other, unwanted, gases cannot accumulate provided the reflector is specific for the chosen anaesthetic. Carbon dioxide absorbers and circle systems, which interfere with the free flow of air between the ventilator and the patient, are therefore not required. The volume of vapour used with an anaesthesia system may be related to the volume of vapour that would have been used in an open system (Efficiency, see Methods). In the first description of the Anaconda, 40% efficiency was reported [19]. With technical modifications, this has been improved to 90% for isoflurane and sevoflurane, over a wide range of concentrations [4]. In the opinion of the authors, efficiency above 80% in the clinically used concentration range would be acceptable for routine use. For the Mirus, we showed 80% efficiency only up to 1.8% desflurane. However, a minor modification, replacing the reflector of the Mirus with a cut-out of the reflector of the Anaconda, led to a significant increase in efficiency. This extended the working range with acceptable efficiency up to the concentration range used clinically. According to the manufacturers, both reflectors consist of activated carbon fibres. However, their preferential absorbing and desorbing characteristics may well be different. They also differ in shape and positioning in the respiratory flow. The reflector of the Anaconda is interwoven with white fibres of a heat moisture exchanger, and appears to act better in this bench study. However, because the study was performed in a bench model, the results may not be directly transferable to clinical practice. Further investigations in patients are needed to evaluate the Mirus in the ICU setting.

In summary, the Mirus appears to be a useful and unique system for the administration of desflurane with common ICU ventilators.

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Competing interests

No other funding and no competing interests declared.

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