Time course of inhaled anaesthetic drug delivery using a new multifunctional closed-circuit anaesthesia ventilator. In vitro comparison with a classical anaesthesia machine

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Background. The aim of this study was to detail the time-course, defined as the changes in end-tidal drug concentration with time, and consumption of inhaled anaesthetics when using a multifunctional closed-circuit anaesthesia machine in various drug delivery modes, and to compare it with a classical anaesthesia machine using an out-of-circle vaporizer under high and low fresh gas flow conditions.

Methods. Using an artificial test lung, sevoflurane and desflurane time-course and consumption were compared when using the Zeus® apparatus (Dräger, Lübeck, Germany) with direct injection of inhaled anaesthetics or the Primus® apparatus (Dräger, Lübeck, Germany) using a classical out-of-circle vaporizer. Anaesthetics were targeted at 1 and 2 MAC end-tidal during 15 min. For both apparatus, out-of-circle high and low fresh gas control (FGC) and for Zeus®, auto-control (AC) modes (fixed fresh gas flow at 6 and 1 litre min⁻¹ and uptake mode) were compared. Time to reach target, initial overshoot and stability at target, and wash-out times were compared.

Results. In FGC, an initial overshoot in end-tidal drug concentration is seen when using 6 litre min⁻¹ fresh gas flow and a slower time course is observed when using only 1 litre min⁻¹ in both apparatus. In auto-control mode, the time course of both sevoflurane and desflurane was very fast and not influenced by the changes in fresh gas flow. No overshoot at target was seen. At all settings, the wash-out times were faster when using Zeus® than Primus®. Inhaled anaesthetic consumption was lowest with the Zeus® ventilator in uptake AC mode.

Conclusion. A combination of the fastest time course and lowest consumption of sevoflurane and desflurane was found when using the Zeus® apparatus in AC uptake mode.


Keywords: anaesthetics, volatile; equipment, ventilators; ventilation, fresh gas flow

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The time course of optimal inhaled anaesthetic drug delivery is hampered by a conflict between reducing agent consumption by minimizing the fresh gas flow (FGF) and levelling the difference between desired and actual drug concentration, particularly when using classical anaesthesia machines. Solid titration of inhaled anaesthetics implies a fast and reliable alteration without overshooting the targeted inhaled agent concentration and involves the maintenance of a stable desired drug level. In contrast, economy of consumption is only possible when minimizing FGF towards low-flow or even closed-circuit conditions, whereby fresh-gas flow equals patient uptake.¹

Classically applied out-of-circle vaporizer setting implies that a fast adjustment of inhaled agent concentration is only feasible by vastly increasing the FGF resulting in a possible overshoot in inhaled agent concentrations and increased consumption.²³ Using a principle where an agent is directly delivered into the breathing circle system independent of FGF theoretically allows fastest alteration of agent

¹Declaration of interest. Dr Manigel and Mr Buschke are employees of Dräger Medical, Lübeck, Germany. The Zeus® ventilator was kindly loaned to the Department of Anaesthesia, Ghent University Hospital by Dräger Medical.
concentration. By uncoupling agent delivery and FGF, the conflict between anaesthetic agent concentration and minimal consumption will be resolved.\textsuperscript{4}

Various experimental systems have been described in the literature seeking these criteria of agent control and delivery while using closed-circuit technology together with in-circle agent delivery.\textsuperscript{5–7} Many disadvantages\textsuperscript{8–10} have limited their introduction into clinical practice. Recently, a new anaesthesia machine (Zeus\textsuperscript{®}, Dräger, Lübeck, Germany) was developed and commercialized aimed at resolving the disadvantages from the experimental generation of closed-circuit machines. This system uses a newly designed, blower-driven ventilator and a servo-controlled valve system to control various ventilation modes. Anaesthetic and fresh gas delivery is feedback-controlled by using direct injection into the breathing circle, making it possible to realize closed-circuit ventilation.

The aim of this study was to investigate the time course and consumption of inhaled anaesthetic \textit{in vitro} when using the Zeus\textsuperscript{®} anaesthesia machine in various drug delivery modes and to compare it with a classical anaesthesia machine using an out-of-circle vaporizer in high and low FGF conditions.

Materials and methods

Description of the applied ventilators

The Zeus\textsuperscript{®} apparatus

The breathing system of the Zeus\textsuperscript{®} apparatus follows the basic structure of a classical rebreathing system (circle system), as shown in Figure 1. The exhaled breathing gas is led through the expiratory limb with the non-return valve to the manual breathing bag, which is used as the breathing gas reservoir of the ventilator. The blower (see below) is speed-controlled and conveys the gas out the breathing bag through the absorber, the non-return valve and the inspiratory flow sensor into the patient’s lungs. The inspiratory pressure is regulated with the blower. When exhalation begins, the proportional controlled valve opens. The gas mixture flows out of the lungs through the expiratory non-return valve and the proportional valve back into the breathing bag. Surplus volume is evacuated through the surplus gas valve (preset at 1 kPa) to the anaesthetic gas scavenger system. The total breathing system volume including soda lime canister is 2 litre (value measured without breathing bag). The ventilation system compliance is around \(0.2\ \text{ml kPa}^{-1}\) (value measured without breathing hoses).

The ventilator consists of an electronic driven and controlled compressor turbine placed in the inspiratory limb. The compressor turbine is dynamically driven by a brushless DC motor, enabling it to: (i) build up the breathing pressure and deliver the corresponding flow to the patient during inspiration time; and (ii) deliver a circuit flow that is required to mix the gas within the breathing system independently from patient inspiratory effort. During automatic ventilation, the turbine transports the breathing gas from the breathing bag reservoir to the patient during the inspiratory phase. During expiration, the gas returns to the bag and is additionally circulated and mixed.

The Direct Injection of Volatile Anaesthetics (DIVA) anaesthetic metering unit meters volatile anaesthetics and FGF, as schematically presented in Figure 2. It comprises the non-anaesthetic-specific supply unit and up to two plug-in, anaesthetic-specific metering units (Fig. 3). The metering

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig1.png}
\caption{Schematic view of the Zeus\textsuperscript{®} breathing system.}
\end{figure}
The supply unit is part of the closed-circuit delivery system. The delivery system is able to work in different operation modes. As explained below, in AC uptake the delivery system injects vapour and fresh gas separately into the breathing system. According to required uptake this fresh gas and volatile anaesthetics are injected. Instead of selecting ‘Uptake’, the user can preset a ‘minimum fresh gas flow’. In the ‘Fresh gas control’ (FGC) mode, the fresh gas is mixed with the anaesthetic agent vapour to emulate a classical ventilation.
system with flow meter and vaporizer. The mixed gas is delivered to the breathing system or optionally to an external fresh gas outlet.

The main sensor system contains various oxygen and infrared analysers to continuously monitor the ventilation and agent delivery systems (see Appendix 1).

The Zeus® apparatus is multifunctional in both administration modes for inhaled anaesthetics and fresh gas, as shown in Table 1, and in ventilation modes. Some of the modes require closed-loop feedback systems, which are explained in detail in Appendix 2. For drug delivery, two control modes are possible, FGC and AC. In FGC mode, a classical ventilator with capacity for low-flow and an out-of-circle vaporizer is emulated and no automated system is active. FGF and oxygen concentration are set manually, emulating the use of classical rotameters. The set concentration (vol%) of inhaled anaesthetics is set at a specific ‘emulated vaporizer’ concentration. In AC mode, multiple computerized closed-loop feedback systems can be turned on. In the AC mode with minimal FGF (e.g. 1 litre min⁻¹), the clinician sets a targeted end-tidal concentration of inhaled anaesthetic and the volatile anaesthetic feedback control will obtain and maintain this targeted end-tidal concentration as accurate as possible, thereby initially overshooting the inspiratory concentration. The oxygen concentration in the breathing circuit is targeted towards a set inspiratory oxygen concentration using the oxygen closed-loop feedback control. In full AC mode, also called ‘uptake mode’, anaesthetic delivery, inspiratory oxygen concentration, and FGF are feedback-controlled. FGF is therefore minimized towards closed-circuit conditions and will only add the required quanta of oxygen, nitrous oxide or air to maintain a given set gas mixture.

The specifications of the feedback controllers and the ventilation modes are detailed in Appendices 2 and 3, respectively.

**The Primus® apparatus**
The Primus® Anesthesia Workstation consists of an electrical piston-driven ventilator, an electronic mixed gas control unit and out-of-circle vaporizers to deliver the volatile anaesthetic. The breathing system of the Primus® apparatus is a classical rebreathing system (circle system).

**In vitro testing**
To simulate clinical conditions, an artificial test lung (Lungensimulator LS8000, Dräger, Lübeck, Germany) was used, into which 0.2 litre min⁻¹ carbon dioxide was introduced, aiming for an end-tidal carbon dioxide partial pressure ($E_{CO_2}'$) of ~5.3 kPa. A continuous flow of 0.2 litre min⁻¹ (simulating oxygen consumption) was sampled to a stand-alone S/5 monitor system (Datex-Ohmeda, Helsinki, Finland) and not returned to the system. Using this, human oxygen consumption and carbon dioxide production was simulated. Additionally, the gas sample line from the Zeus® or Primus® apparatus (depending on the study group) was connected at the Y-piece of the breathing circle for obligatory gas sampling. These gas samples are returned into the breathing system resulting in no gas loss.

The artificial lung model is already described and used elsewhere.11

For each test-run, carbon dioxide absorbent (Drägersorb 800, Dräger, Lübeck, Germany) was renewed. Only oxygen and air was used in the breathing system. The ventilatory frequency was set at 12 bpm and the tidal volume at 0.49 litre. After checking the air tightness of the ventilator (this is part of the installation procedure), it was connected to the artificial lung. In FGC (Primus® and Zeus®), the fresh gas was set at oxygen 50% in nitrogen. In AC (Zeus® only), the inspiratory oxygen was set at 50% in nitrogen. First, the lung was ventilated until a stable profile of capnography and inspiratory oxygen concentration was attained, simulating adequate preoxygenation. Thereafter, the test was started.

Each test-run consists of three stages: at time 0, the aim is to achieve and maintain an end-tidal concentration of 1 MAC (i.e. 2% for sevoflurane and 6% for desflurane). Thereafter, at time 15 min, the ventilator is reset to achieve and maintain an end-tidal concentration of 2 MAC (i.e. 4% for sevoflurane and 12% for desflurane); and finally, at time 30 min, the volatile anaesthetic administration was stopped and agent is blown-off. Recording stopped when end-tidal level fell below 0.2 MAC. During each test-run, ventilator settings were maintained unchanged; only the fresh-gas percentage (FGC) or the set end-tidal percentage (AC) of volatile anaesthetic were adjusted.

As summarized in Table 2, using the Zeus® apparatus, five different settings were used for each agent (sevoflurane and desflurane): FGC 1 litre FGF; FGC 6 litre FGF; AC 1 litre FGF; AC 6 litre FGF; and AC uptake mode, in which FGF equals consumption. Using the Primus® apparatus, only the two FGC modes were used. In FGC, the anaesthetist manually titrated the vaporizer towards the targeted level. This was done by first setting the vaporizer at a maximum

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**Table 1** The Zeus® apparatus. FGF, fresh gas flow; FGC, fresh gas control; AC, auto-control.

<table>
<thead>
<tr>
<th>Agent delivery</th>
<th>FGF</th>
<th>Fresh gas oxygen concentration in breathing circle</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGC</td>
<td>Manually set by the anaesthetist at a specific ‘vaporizer’ concentration</td>
<td>Manually set by the anaesthetist at a fixed flow (litre min⁻¹)</td>
</tr>
<tr>
<td>AC constant flow</td>
<td>Feedback control targeted towards a set end-tidal concentration</td>
<td>Feedback control targeted towards a set inspiratory oxygen concentration</td>
</tr>
<tr>
<td>AC uptake</td>
<td>Feedback control targeted towards a set end-tidal concentration</td>
<td>Feedback control targeted towards a set inspiratory oxygen concentration</td>
</tr>
</tbody>
</table>
concentration (8% for sevoflurane and 18% for desflurane) until the target end-tidal inhaled anaesthetic concentration was reached. Vaporizer settings were then titrated in step changes of 0.3–0.5 vol % in order to maintain the targeted end-tidal inhaled anaesthetic concentration. In AC mode (Zeus/C210 only), drug administration needed to reach and maintain the targeted end-tidal concentration was performed automatically. Each setting was repeated five times.

Both anaesthesia machines and the S5-monitor were connected to a PC for data management at a sampling rate of 1 Hz using Rugloop II/C210 data-manager software (Demed, Temse, Belgium). Before and after each test-run, total vaporizer weight was measured to an accuracy of 0.1 g (Mettler Toledo/C210 balance PG8001-S) for precise determination of total volatile anaesthetic consumption. To calculate the amount of liquid volatile anaesthetic, the following formula was used:

\[
\text{Volume of inhaled anaesthetic agent (litres)} = \frac{\text{Weight of used anaesthetic agent (kg)}}{\text{Specific weight (kg litre}^{-1})}
\]

The specific weight for sevoflurane is 1.52 kg litre\(^{-1}\) and 1.465 kg litre\(^{-1}\) for desflurane.\(^{12}\)

**Performance measures and statistical comparison**

Different end-points were analysed and compared:

(i) *Time to 0.9 MAC and 1.9 MAC* defined as the number of seconds needed to reach end-tidal concentrations of 0.9 and 1.9 MAC, respectively.

(ii) *Overshoot at 1 MAC and at 2 MAC* defined as the highest value in end-tidal agent content when aiming for 1 and 2 MAC, respectively.

(iii) *Stability at steady-state* defined as the percentage of end-tidal agent values that are in the range of 1 ± 0.1 MAC and 2 ± 0.1 MAC, respectively. Stability is evaluated from 7 to 15 min for 1 MAC, and from 22 to 30 min for 2 MAC after initiation of the procedure.

(iv) *Time to 25, 50, 75, and 90% wash-out* defined as the number of seconds needed after starting blow-off to attain a 25, 50, 75 and 90% reduction of end-tidal agent concentration, respectively.

(v) *Total agent consumption* defined as the total volume in millilitres of agent consumed during the whole procedure, measured using a balance.

Statistical analysis was performed using repeated-measures ANOVA, followed by Tukey-Kramer multiple comparison test if required. Significance level was set at \(P<0.05\). All statistics were performed using Graphpad Instat 3.0 for Windows (GraphPad Software, San Diego, CA, USA).

**Results**

Data from all runs were included in the final analysis. For each setting, the time course of the mean end-tidal concentration is plotted in Figures 4 and 5 for sevoflurane and desflurane, respectively. Part A of both figures shows the FGC settings for both anaesthesia machines. For both anaesthetics, an initial overshoot in end-tidal drug concentration is seen when using high FGF (6 litre min\(^{-1}\)) and a slower time course is observed when using only 1 litre min\(^{-1}\). For the Zeus\(^{\circledR}\) apparatus in AC mode, similar mean time courses of inhaled anaesthetic were observed for all settings (Figs 4B and 5B).

For both anaesthesia machines, the various performance end-points calculated on the end-tidal drug concentration
for the runs during AC with 1 and 6 litre min$^{-1}$/C0/C210.

The characteristics of the breathing system and the technique of inhaled anaesthetic and carrier gas administration is greatly influenced by the characteristics of the breathing system and the technique of inhaled anaesthetic and carrier gas administration. When using a classical out-of-circle vaporizer setting, a fast adjustment of the pressure in the rebreathing bag is $<1$ mbar.

Discussion
We have shown that the time course of end-tidal inhaled drug concentration and the consumption of liquid sevoflurane or desflurane is greatly influenced by the characteristics of the breathing system and the technique of inhaled anaesthetic and carrier gas administration. When using a classical out-of-circle vaporizer setting, a fast adjustment of

In this study, a new closed-circuit anaesthesia apparatus with direct injection of volatile anaesthetic and carrier gas into the breathing system has been compared with a classical anaesthesia machine. To address safety issues, we decided to test the characteristics of this new device using a validated in vitro setting simulating inhaled anaesthetic uptake and carbon dioxide production. When comparing the time course of sevoflurane or desflurane end-tidal concentrations in FGC mode from the Zeus apparatus with the classical Primus system, we found that the time to reach 90% of the targeted end-tidal gas concentration was shortest when using high FGF. Therefore, the Primus apparatus, using a classical out-of-circle vaporizer, required less time to reach target than the Zeus apparatus, using a direct injection system. In both anaesthesia machines, this mode resulted in the largest initial overshoot in end-tidal concentration. In contrast, the onset times when using low FGF (1 litre min$^{-1}$) resulted in the longest times to reach target in both anaesthesia machines. Less overshoot was seen than when using low FGF. As already known when using classical out-of-circle vaporizers, the consumption of liquid sevoflurane or desflurane parallels and is influenced by the applied FGF. This was also revealed in this study as seen in Table 5. When comparing the time course for end-tidal concentration in 1 litre min$^{-1}$ and 6 litre min$^{-1}$ FGC mode for both anaesthesia machines, the times to reach 0.9 and 1.9 MAC were always shorter when using the Primus apparatus vs the Zeus apparatus. This is attributable to the fact that in the Primus, because there is no blower, fresh gas partly goes directly to the patient, while in Zeus, fresh gas is extensively mixed within the circle volume before reaching the patient.

For the Zeus apparatus, the results in FGC were compared with various settings in AC mode. In the full automated mode, the apparatus reaches closed-circuit conditions. In a closed-circuit, the FGF equals the patient’s uptake. Closed-circuit conditions have been defined by Baum in either non-quantitative anaesthesia, whereby consistency of gas volume but not necessarily of anaesthetic gas composition is obtained in the breathing circuit, and in quantitative anaesthesia, whereby both of these factors are constant during the entire anaesthetic period. The latter is only possible if both aspects are controlled electronically by closed-loop feedback. In the Zeus apparatus, when using ‘uptake AC mode’, both fresh gas volume and oxygen concentration are feedback-controlled. Additional fresh gas (oxygen, nitrous oxide/air) will only be delivered when the measured concentrations are lower than the target or when the pressure in the rebreathing bag is $<1$ mbar.
Recently, Versichelen and colleagues 18 described higher
results of the test-runs on both ventilators using desflurane. Results are presented as mean (SD) values for the five test-runs:

| Table 3 | Results of the test-runs on both ventilators using sevoflurane. Results are presented as mean (sd) values for the five test-runs. FGC, fresh gas control; FGF, fresh gas flow; AC, auto-control |
|---------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                | Time to MAC (s) | Overshoot (vol %) | Stability |
|                                | 0.9 MAC | 1.9 MAC | 1 MAC | 2 MAC | 1 MAC | 2 MAC |
|                                |         |         |       |       |       |       |
| Zeus®                          |         |         |       |       |       |       |
| FGC                            |         |         |       |       |       |       |
| 1 litre min⁻¹ FGF              | 228 (15) | 261 (21) | 2.4 (0.2) | 4.1 (0.1) | 80 (18) | 66 (21) |
| 6 litre min⁻¹ FGF              | 76 (5)∗  | 76 (7)∗  | 2.7 (0.3) | 4.3 (0.3) | 99 (3)  | 99 (1)∗ |
| AC                             | 1 litre min⁻¹ FGF | 122 (6)†  | 105 (3)†  | 2.2 (0.1) | 4.3 (0.1) | 100 (0)∗ | 97 (3)∗ |
|                                | 6 litre min⁻¹ FGF | 122 (14)‡  | 103 (10)‡  | 2.2 (0)‡  | 4.2 (0.1) | 100 (0)∗ | 100 (0)∗ |
|                                | Uptake mode | 123 (8)§  | 103 (8)§  | 2.3 (0)§  | 4.3 (0.1) | 95 (7)  | 100 (0)∗ |
|                                | Primus® FGC | 218 (21)†‡  | 267 (9)†‡  | 2.4 (0.2) | 4.1 (0.1) | 45 (17)†‡  | 85 (16) |
|                                | 6 litre min⁻¹ FGF | 54 (1)‡‡  | 65 (3)‡‡  | 2.7 (0.3)‡‡  | 4.3 (0.2) | 100 (0)∗ | 100 (0)∗ |
|                                | 1 FGF and other groups; # P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Primus® and other groups |
|                                | 6 litre min⁻¹ FGF | 40 (3)§  | 67 (5)§  | 122 (6)§  | 207 (3)§  | 213 (4)§  | 327 (6)§  |
|                                | Uptake mode | 47 (7)†‡  | 78 (8)†‡  | 133 (6)†‡  | 212 (6)†‡  | 213 (4)§  | 327 (6)§  |
|                                | Primus® FGC | 186 (7)†‡  | 439 (11)†‡  | 922 (38)†‡  | 1629 (93)†‡  | 1629 (93)†‡  | 1629 (93)†‡  |
|                                | 6 litre min⁻¹ FGF | 54 (5)†‡  | 79 (2)†‡  | 131 (3)†‡  | 221 (5)†‡  | 221 (5)†‡  | 221 (5)†‡  |
|                                | 1 FGF and other groups; # P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Primus® and other groups |
|                                | 6 litre min⁻¹ FGF | 44 (4)‡  | 67 (4)‡  | 113 (4)‡  | 179 (7)‡  | 214 (34)§  | 321 (16)§  |
|                                | Uptake mode | 49 (4)‡  | 81 (11)‡  | 136 (14)‡  | 214 (34)§  | 321 (16)§  | 321 (16)§  |
|                                | Primus® FGC | 186 (7)†‡  | 439 (11)†‡  | 922 (38)†‡  | 1629 (93)†‡  | 1629 (93)†‡  | 1629 (93)†‡  |
|                                | 6 litre min⁻¹ FGF | 54 (5)†‡  | 79 (2)†‡  | 131 (3)†‡  | 221 (5)†‡  | 221 (5)†‡  | 221 (5)†‡  |
|                                | 1 FGF and other groups; # P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Primus® and other groups |

| Table 4 | Results of the test-runs on both ventilators using desflurane. Results are presented as mean (sd) values for the five test-runs. FGC, fresh gas control; FGF, fresh gas flow; AC, auto-control |
|---------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                | Time to MAC (s) | Overshoot (vol %) | Stability |
|                                | 0.9 MAC | 1.9 MAC | 1 MAC | 2 MAC | 1 MAC | 2 MAC |
|                                |         |         |       |       |       |       |
| Zeus®                          |         |         |       |       |       |       |
| FGC                            |         |         |       |       |       |       |
| 1 litre min⁻¹ FGF              | 178 (12) | 384 (5) | 769 (19) | 1325 (31) |
| 6 litre min⁻¹ FGF              | 67 (2)∗  | 119 (6)∗ | 206 (13)∗ | 321 (16)∗ |
| AC                             | 44 (4)†  | 67 (4)†  | 113 (4)†  | 179 (7)†  |
|                                | 49 (4)‡  | 81 (11)‡  | 136 (14)‡  | 214 (34)‡  |
|                                | 47 (7)†‡  | 78 (8)†‡  | 133 (6)†‡  | 212 (6)†‡  |
|                                | Primus® FGC | 186 (7)†‡  | 439 (11)†‡  | 922 (38)†‡  | 1629 (93)†‡  | 1629 (93)†‡  |
|                                | 6 litre min⁻¹ FGF | 54 (5)†‡  | 79 (2)†‡  | 131 (3)†‡  | 221 (5)†‡  | 221 (5)†‡  |
|                                | 1 FGF and other groups; # P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Zeus® and other groups; P < 0.05 between Primus® and other groups |

Previously published, experimental closed-circuit anaesthesia systems used a ‘leak-free’ classical valve circuit whereby the fresh gas flow was reduced to equal the patient’s uptake. Several disadvantages were described with these systems. Accumulation of non-anaesthetic gases like methane, acetone and nitrogen was found.16 17 Recently, Versichelen and colleagues18 described higher absorbent temperatures resulting in higher compound A formation during closed-circuit sevoflurane administration using a classic valve circuit than when using a high-flow valveless closed-circuit system (Physioflex® apparatus, Dräger, Lübeck, Germany).19 In the newly developed Zeus® apparatus, a dynamically driven blower is used to both generate a circuit flow and to generate a breathing pressure in combination with the proportional valve located in the expiratory limb, when required. In contrast to previous systems, no other hardware is required to build up the ventilator.
For patient groups with increased fractions of foreign and trace gases in the exhalation, a fresh gas flow <1 litre min\(^{-1}\) min is contraindicated.\(^{20}\) Therefore, an ‘AC mode with minimal fresh gas flow’ was installed into the Zeus\(^{\circ}\) apparatus. In this mode, equivalent to ‘uptake’ mode, the inhaled anaesthetic and the oxygen delivery are feedback-controlled as described below.

When closed-circuit techniques are used in conjunction with a conventional out-of-circle vaporizer, it is impossible to deliver enough inhaled anaesthetic agent safely into the circuit within a reasonable time.\(^{21}\) Therefore, methods using direct injection of anaesthetic agent into the breathing system have some definitive advantages when compared with the plenum vaporizers. This injection is totally independent from the FGF,\(^{22}\) so even in closed-circuit conditions, rapid changes in concentrations are possible. In our study, when comparing the uptake AC mode with the two fixed-FGF AC modes, no differences in the time course of the end-tidal concentrations were observed (Figs 4b and 5b) for both sevoflurane and desflurane. The consumption of inhaled anaesthetics was only dependent on the set FGF. When using the Zeus\(^{\circ}\) apparatus in ‘uptake AC mode’ only very small quantities of inhaled anaesthetics are used. This is in contrast to the out-of-circle vaporizers (or FGC when using the Zeus\(^{\circ}\)) where low fresh gas flow will delay changes in inhaled anaesthetic concentrations. When comparing the stability at equilibrium for all modes (Tables 3 and 4), results are excellent except for the 1 litre min\(^{-1}\) FGF during FGC mode for both anaesthesia machines. This is largely attributable to its slow response to changes in operator settings. One can conclude that low-flow FGC is not adequate when a swift change in agent is desired. Remarkably, low-flow and uptake conditions in AC are responsive to rapid adjustments of agent concentration.

Although calculated fixed-rate administration of direct injected inhaled anaesthetics using an uptake formula has been described,\(^{7,23}\) adaptive control of direct injection of inhaled anaesthetics has become state-of-the-art. Therefore, the feedback controller measures the end-tidal inhaled anaesthetic concentration and titrates the direct anaesthetic injection to reach and maintain the targeted end-tidal concentration as soon and accurate as possible. This facilitates and secures inhaled anaesthetic drug administration as seen when using the Zeus\(^{\circ}\) ventilator. Only a few steps were required to guide drug administration, in contrast to the manually controlled ‘FGC mode’ where continuous changes in agent titration are required to reach and maintain a targeted concentration. Though stability is satisfactory in all modes, one must consider this to be an in vitro study, where operator attention exclusively goes to the ventilator settings. In daily practice, there are many other responsibilities requiring attention. While stability in AC mode will not alter when the operator is distracted from the ventilator settings, in FGC it can do so dramatically.

Time to washout, again, is highly comparable within the three AC settings of the Zeus\(^{\circ}\) apparatus. Because the ventilator automatically maximizes FGF to enhance flushing of the breathing system until a new set value is reached, the AC mode is always faster in decreasing agent content of the system than fresh gas control mode. Interestingly in AC, washout at 1 litre min\(^{-1}\) FGF is faster than at 6 litre min\(^{-1}\) FGF and uptake mode, although differences are small. Emergence times may be expected to be much shorter when working in AC than in FGF. Only when vastly increasing FGF, will emergence times approximate those in AC. Times to washout in FGC mode with Zeus\(^{\circ}\) were faster than with Primus\(^{\circ}\).

In conclusion, when investigating the time course and consumption of inhaled anaesthetic drug concentration during in vitro conditions using the Zeus\(^{\circ}\) apparatus in various drug delivery modes and when comparing it with a classical anaesthesia machine using an out-of-circle vaporizer in high and low FGF conditions, we found that the ability of the Zeus\(^{\circ}\) apparatus to provide AC allows the operator to have a very fast and reliable induction of volatile agent anaesthesia with minimal overshoot. It also allows a stable profile of desired end-tidal agent concentrations with minimal or no operator intervention. Moreover, because elimination of the inhaled agent is optimized when using the Zeus\(^{\circ}\) apparatus, times to washout were short even in closed-circuit settings. In addition, uptake mode allows minimal consumption of volatile anaesthetic, while not compromising the time course of inhaled agent end-tidal concentrations. Optimizing and harmonizing patient safety, operator comfort and economic and ecologic considerations, this machine may set a new level of quality in ventilation anaesthesia.

### Appendix 1

#### Specifications of the main sensor systems

The paramagnetic oxygen analyser, type ServoMox (M&C, Ratingen, Germany) is a null deflection type. Non-linearity
is 0.1 vol%; zero drift is <0.003 vol % week\(^{-1}\); temperature drift is <0.002 vol % K\(^{-1}\). The sampling gas (200 ml min\(^{-1}\)) for oxygen and volatile anaesthetic measurement is completely returned to the system. The infrared gas analyser is a side-stream 5-channel infrared spectrometer (IRIA-Version, Dräger Medical, Lübeck, Germany) with automatic agent recognition and monitors the capnogram (carbon dioxide), the inspiratory nitrous oxide concentrations and the in- and expiratory concentrations of volatile anaesthetics by sampling from the Y-piece. The analyser has an accuracy of 5% of the measured value. The response time (t 10...90) is 350 ms.

The ventilator and agent-delivery systems are monitored continuously by a protection system that is not only monitoring but also has means to switch the system into a safe operating mode. The system uses additional redundant sensors and computers, so that common mode failures are prevented. The most important protection tasks are:

(i) To prevent too high volatile anaesthetic concentrations, an additional side stream infrared agent sensor (Dräger ILCA Version, Dräger, Lübeck, Germany) monitors the breathing gas in the inspiratory limb of the breathing circle.

(ii) To prevent a too low oxygen concentration, an additional side stream oxygen sensor monitors the breathing gas in the inspiratory gas line. The sensor uses a non-disposable cell technology (Dräger Oxytrace Type A). A constant voltage is applied to an electrochemical cell and the current of the cell is proportional to the oxygen concentration.

(iii) To prevent a too high ventilation pressure, two pressure sensors located at the inspiratory and expiratory side of the breathing system continuously monitor the airway pressure. If the pressure is >5 hPa above set values the airway pressure is released to the ambient pressure. Additionally, a mechanical high-pressure valve located at the inspiratory line limits the maximum pressure to 80 hPa.

**Appendix 2**

**Specifications of the feedback-controllers**

**Volatile anaesthetic feedback control**

A robust model-based feedback-controller is used to achieve the set end-tidal agent concentration. Provided that a circuit flow (of about 12 litre min\(^{-1}\), see above) leads to a homogeneous gas concentration in the breathing system, the design can be reduced to a simple volume model whereby:

(i) the system volume (vol\(_{sys}\)), is composed of the breathing system volume including the absorber, the bag and the hoses; and

(ii) the patient, who is simply modelled by his functional residual capacity (FRC) with a homogeneous gas concentration. The FRC is estimated from the patient settings height in meter, age in years and sex as follows:

\[
\text{Male FRC} = (2.34 \times \text{height}) + (0.009 \times \text{age}) - 1.09
\]

\[
\text{Female FRC} = (2.24 \times \text{height}) + (0.001 \times \text{age}) - 1.00
\]

The following measurements are taken to determine the agent concentration in the breathing system and the agent concentration in the patient lung: (i) the inspiratory agent concentration (insp\(_{agent}\)) is measured for safety reasons inside the breathing system and at the Y-piece; and (ii) the end-tidal agent concentration (exp\(_{agent}\)), which corresponds to the agent concentration inside the patient lung, is measured at the Y-piece. For safety reasons the value is only valid, if a valid carbon dioxide-signal is detected. If no carbon dioxide breathing cycles are detected, the end-tidal agent concentration will be replaced by the inspiratory agent concentration, which leads to less feedback control performance.

The output of the feedback controller consists of the following parts:

(i) The amount of agent necessary to bring up the concentration inside the breathing system to an inspiratory concentration:

\[
\text{insp}_{agent} = \text{set}_{exp} - \text{insp}_{agent} \times \text{vol}_{sys}.
\]

The agent flow is calculated from the amount of agent considering the time delay (T\(_{delay}\)) of the agent measurement as well as the delay of the agent dose unit:

\[
\text{insp}_{agentflow} = \text{insp}_{agent} \times \text{vol}_{sys} / \text{T}_{delay}.
\]

(ii) The amount of agent necessary to bring up the concentration inside the patient lung to the desired end-tidal concentration:

\[
\text{exp}_{agent} = \text{set}_{exp} - \text{exp}_{agent} \times \text{FRC} \times \text{agentflow} / \text{T}_{delay}.
\]

(iii) The agent flow necessary to balance the agent uptake by the patient is calculated by a traditional integral action controller:

\[
\text{uptake}_{agentflow} = \text{controller} (\text{set}_{exp} - \text{exp}_{agent})
\]

To ensure, that the inspiratory agent concentration will not rise above the maximum inspiratory set value (set\(_{inspmax}_{agent}\)) the total flow:

\[
\text{sum}_{agent} = \text{insp}_{agent} + \text{exp}_{agentflow} + \text{uptake}_{agentflow},
\]

is limited against:

\[
\text{max}_{agent} = \text{set}_{inspmax} - \text{insp}_{agent} \times \text{vol}_{sys} / \text{T}_{delay}.
\]
If FGF is set by the user, the oxygen feedback-controller or the oxygen uptake controller, the disturbance is minimized by giving an additional proportional agent flow:

\[ FGF_{agentflow} = FGF \times \text{set}_{\text{exp}}_{\text{agent}}. \]

If the controller detects that the actual expiratory concentration is higher than the set value, the system is flushed with a high FGF and thus washed out to the scavenging system. This is the case at the end of a procedure where the required concentration is decreased.

**Oxygen feedback control**

The oxygen supply system is based on the measurement of the concentration in the system and the comparison of measured and set values. A robust model-based feedback-controller is used to achieve the set inspiratory oxygen concentration. Provided that a circuit flow of \(~ 12 \text{ litre min}^{-1}\) leads to a homogeneous gas concentration in the breathing system, the design can be reduced to a simple continuous flow model considering the circuit flow (\(F_{\text{circ}}\)) and the minute ventilation flow (AMV).

The following measurements are taken to determine the oxygen concentration in the breathing system as the input values of the feedback controller: (i) the inspiratory oxygen concentration (\(\text{insp}_{\text{oxygen}}\)) is measured for safety reasons inside the breathing system and at the Y-piece; and (ii) the end-tidal oxygen concentration (\(\text{exp}_{\text{oxygen}}\)), which is, from the feedback controller’s point of view, a disturbance to the concentration in the breathing system, measured at the Y-piece. For safety reasons, the value is only valid if a valid carbon dioxide signal is detected. If no carbon dioxide breathing cycles are detected, the end-tidal oxygen concentration will be replaced by the inspiratory oxygen concentration, which leads to less feedback-control performance.

The output of the feedback-controller is the amount of FGF, which consists of the following parts:

(i) A first term considering the concentration inside the breathing system represented by \(F_{\text{circ}}\):

\[ F_{\text{circ}}_{\text{FGF}} = (\text{set}_{\text{insp}}_{\text{oxygen}} - \text{insp}_{\text{oxygen}}) \times F_{\text{circ}}. \]

A second term considering the concentration in the exhaled breathing gas represented by AMV:

\[ \text{AMV}_{\text{FGF}} = (\text{set}_{\text{insp}}_{\text{oxygen}} - \text{exp}_{\text{oxygen}}) \times \text{AMV}. \]

A third term, which is the output of a traditional PI-feedback controller:

\[ \text{control}_{\text{FGF}} = \text{controller} (\text{set}_{\text{insp}}_{\text{oxygen}} - \text{insp}_{\text{oxygen}}). \]

Together this leads to:

\[ \text{sum}_{\text{FGF}} = F_{\text{circ}}_{\text{FGF}} + \text{AMV}_{\text{FGF}} + \text{control}_{\text{FGF}}. \]

The oxygen concentration \((\text{oxygenconc}_{\text{sum}}_{\text{FGF}})\) of the FGF calculated by the oxygen feedback-control is always either 21 or 100 vol % depending on the following criteria:

If \(\text{sum}_{\text{FGF}} > 0\): the oxygen concentration of fresh gas flow is 100 vol %.

If \(\text{sum}_{\text{FGF}} < 0\): the oxygen concentration of fresh gas flow is 21 vol % (add nitrogen or nitrous oxide).

Regardless of the chosen carrier gas (nitrous oxide or air) the oxygen concentration of the FGF will never be <21 vol %.

Considering the diversity of the gain depending on the target oxygen concentration, this leads to the total flow \((\text{total}_{\text{FGF}})\), which is limited to a maximum flow of 12 litre min\(^{-1}\):

\[ \text{total}_{\text{FGF}} = \text{sum}_{\text{FGF}} / (\text{conc}_{\text{sum}}_{\text{FGF}} - \text{set}_{\text{insp}_{\text{oxygen}}}). \]

\[ \text{oxygenconc}_{\text{total}}_{\text{FGF}} = \text{oxygenconc}_{\text{sum}}_{\text{FGF}}. \]

Therefore, it is assumed, that owing to the circuit flow of around 12 litre min\(^{-1}\) a fresh gas flow of 12 litre min\(^{-1}\) is optimum, and a flow of >12 litre min\(^{-1}\) increases the wastage of fresh gas more than the speed of the concentration change.

When choosing a minimum flow (\(F_{\text{min}}\)) above uptake, the FGF is downwardly limited to the set minimum flow. The oxygen concentration of the resulting FGF is calculated as:

If \( F_{\text{min}} < \text{total}_{\text{FGF}} \):

\[ F_{\text{GF}} = \text{total}_{\text{FGF}} \times \text{oxygenconc}_{\text{sum}}_{\text{FGF}} = \text{oxygenconc}_{\text{total}}_{\text{FGF}} \]

If \( F_{\text{min}} > \text{total}_{\text{FGF}} \):

\[ F_{\text{GF}} = F_{\text{min}} \times \text{oxygenconc}_{\text{total}}_{\text{FGF}} + (\text{total}_{\text{FGF}} \times \text{oxygenconc}_{\text{total}}_{\text{FGF}}) / F_{\text{min}}. \]

**Volume feedback control**

If the minimal flow setting is set to ‘uptake’ and the oxygen concentration is ~3 vol % above or below the set value, the feedback-controller switches its priority from oxygen to volume feedback control.

In a balanced closed breathing system, the fresh gas including anaesthetic vapour is equal to the gas uptake of the patient and leakage loss. This is obtained by measuring the pressure of the breathing bag from breath to breath at the end of expiration. A feedback-controller delivers a FGF to the system in order to keep the end-expiratory pressure in the breathing bag constant at 1 mbar. This way, the volume of the breathing system remains constant and the system is balanced.

Using the signal of the oxygen analyser, the computer calculates the required oxygen partition in the delivered fresh gas as described above. Both control algorithms together determine the required amount of oxygen. In a
continuous process these two algorithms keep the system volume and the inspiratory oxygen concentration stable.

Only when there is no leak, no gas wash-out or agent wash-in, does oxygen flow reflect the patient’s oxygen uptake. When nitrogen is washed out from the patient or when agent is washed into the patient, the oxygen concentration will drop. If the oxygen concentration drops $>3$ vol % below the set concentration, the system valves will no longer stay closed and the priority is switched back to oxygen concentration. However, the trend of the oxygen flow is stored and can give information about changes in patient uptake. Besides the estimation of oxygen uptake, the uptake mode leads to less agent consumption.

Owing to the concept used to measure the pressure of the breathing bag volume, feedback control is not available in manual spontaneous ventilation.

**Appendix 3**

**Ventilation modes**

As mentioned above, the blower and the proportional controlled PEEP-valve together assure a certain ventilation pressure and a certain circuit flow at the same time. Whenever the blower is pressure controlled, the PEEP-valve is flow controlled and vice versa. Circuit flow is the main precondition for dosing agent directly into the breathing system and for the characteristics of the oxygen feedback-controller as well as the agent feedback-controller described below.

However, during the inspiration phase, the amount of the circuit flow that could be measured with the expiratory flow sensor is negligible in mandatory controlled ventilation whether pressure- or volume-controlled.

**Pressure-controlled ventilation**

From its nature, the Zeus® is designed for pressure-controlled, and pressure-augmented, ventilation modes (e.g. pressure support). The blower, as the key component of the ventilator, is a pressure source with a breathing-through resistance of $\sim 2–3$ mbar litre$^{-1}$ s$^{-1}$. The maximum set value for the inspiratory pressure is 50 mbar, which is generated by the blower at a speed of about 30 000 r.p.m. Although the blower has a low breathing-through resistance, it is feedback-controlled by the expiratory pressure sensor during the inspiration phase to overcome the inspiratory breathing resistances of the absorber, the blower and the inspiratory hoses. During the expiratory phase, the primary task of the blower is to guarantee a circuit flow of $\sim 18$ litre$^{-1}$ min. Therefore, it is feedback-controlled by the inspiratory flow sensor, whereas the PEEP-valve guarantees the set PEEP value.

**Flow/volume-controlled ventilation**

The ventilator offers two different volume-controlled ventilation modes. In both modes, the tidal volume is feedback-controlled by the inspiratory flow sensor. The preferred volume controlled ventilation mode in Zeus® should be ‘AutoFlow’ with a pressure/flow waveform equivalent to pressure-controlled ventilation. Therefore, the inspiratory pressure level is calculated in a breath-by-breath feedback control loop from the set tidal volume and the inspiratory tidal volume measured by the internal inspiratory flow sensor. As such, ‘AutoFlow’ guarantees the application of the adjusted volume by gradual adaptation of the mechanical inspiration pressure to the lung conditions. Spontaneous breathing is possible at any time also on the inspiratory pressure level—as in pressure-controlled ventilation.

The other controlled ventilation mode is emulating classical volume-controlled ventilation with a constant inspiratory flow and a plateau phase. In this ventilation mode, a feedback-controller, based on the signal of the inspiratory flow sensor, enables the blower to act like a piston-driven ventilator.

The expiratory phase in both volume-controlled ventilation modes is equivalent to that in pressure-controlled ventilation.

**Manual/spontaneous ventilation**

The Zeus® apparatus is able to assure a PEEP during manual/spontaneous ventilation, which differs from conventional anaesthesia machines. Therefore, the PEEP valve is set to the desired CPAP level and the blower is feedback-controlled by the internal flow sensors. To assure a superposed circuit flow the blower is feedback-controlled by the expiratory flow sensor during inspiration and it is feedback-controlled by the inspiratory flow sensor during expiration.

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