End-tidal control vs. manually controlled minimal-flow anesthesia: a prospective comparative trial

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Conflicts of interest
Martin Bauer received lecture honoraria from the congress organization during meetings where part of this study has been presented (DAC, Leipzig, Germany 2014; ESA, Stockholm, Sweden 2014; HAI, Berlin, Germany 2014; NAT, Hamburg, Germany 2014; Athens, Greece 2014). Martin Bauer is also a member of the GE Healthcare Clinical Advisory Board. For the remaining authors no conflicts of interests were declared.

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Trial registration: DRKS00005800, http://apps.who.int/trialsearch/

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Background: To ensure safe general anesthesia, manually controlled anesthesia requires constant monitoring and numerous manual adjustments of the gas dosage, especially for low- and minimal-flow anesthesia. Oxygen flow-rate and administration of volatile anesthetics can also be controlled automatically by anesthesia machines using the end-tidal control technique, which ensures constant end-tidal concentrations of oxygen and anesthetic gas via feedback and continuous adjustment mechanisms. We investigated the hypothesis that end-tidal control is superior to manually controlled minimal-flow anesthesia (0.5 l/min).

Methods: In this prospective trial, we included 64 patients undergoing elective surgery under general anesthesia. We analyzed the precision of maintenance of the sevoflurane concentration (1.2–1.4%) and expiratory oxygen (35–40%) and the number of necessary adjustments.

Results: Target-concentrations of sevoflurane and oxygen were maintained at more stable levels with the use of end-tidal control (during the first 15 min 28% vs. 51% and from 15 to 60 min 1% vs. 19% deviation from sevoflurane target, \( P < 0.0001 \); 45% vs. 86% and 5% vs. 15% deviation from \( O_2 \) target, \( P < 0.01 \), respectively), while manual controlled minimal-flow anesthesia required more interventions to maintain the defined target ranges of sevoflurane (8, IQR 6–12) and end-tidal oxygen (5, IQR 3–6). The target-concentrations were reached earlier with the use of end-tidal compared with manual controlled minimal-flow anesthesia but required slightly greater use of anesthetic agents (6.9 vs. 6.0 ml/h).

Conclusions: End-tidal control is a superior technique for setting and maintaining oxygen and anesthetic gas concentrations in a stable and rapid manner compared with manual control. Consequently, end-tidal control can effectively support the anesthetist.

Editorial Comment
The management of volatile anaesthesia agent levels in low-flow conditions has usually been done through manual changes made at the gas flow. This clinical study demonstrates that automatic anesthesia machine end-tidal control of volatile anesthetics and oxygen supply simplifies low-flow anaesthesia management in a precise manner.
Modern anesthesia machines use circular systems in which ventilated gas re-circulates to a certain degree and is therefore reused, preserving temperature, and humidity. The rebreathing fraction is increased by a reduction in fresh gas flow, which leads to a considerable decrease in consumption of fresh gas and volatile anesthetics, resulting in reductions in cost and atmospheric pollution. In a closed ventilation system, only the patient’s requirements for oxygen and anesthetic agents are supplemented.

A fresh gas flow-rate of 0.5 l/min is defined as the minimal-flow technique. The oxygen and anesthetic gas titration can be manually controlled by the anesthetist. To assure safe and appropriate anesthesia, manually controlled anesthesia requires constant monitoring and numerous adjustments to the gas dosage by the anesthetist, especially for low- and minimal-flow anesthesia. Oxygen flow and volatile anesthetics can also be automatically controlled by anesthesia machines using end-tidal control, which ensures constant end-tidal concentration of oxygen and anesthetic gas via feedback and continuous automatic adjustment mechanisms. Anesthesiologists needing to make fewer interventions during a case may have clinical importance in terms of distraction, record keeping and patient safety.

In this prospective trial, we compared the automatic end-tidal control technique to manual control/minimal flow anesthesia using the same type of anesthesia machine. The aim of this study was to investigate the hypothesis that end-tidal control anesthesia is superior to manual control-minimal flow anesthesia and that it is an effective technique to support the anesthetist. We analyzed whether there are differences when comparing end-tidal control to manual control-minimal flow anesthesia with respect to reaching and maintaining target-concentrations of sevoflurane and oxygen and the consumption of volatile anesthetics. We further analyzed the workload of the anesthetists by determining how many interventions were necessary in manual control-minimal flow anesthesia.

**Methods**

The trial was approved by the local ethics committee (Ethikkommission Universitätsmedizin Göttingen, N° 6/9/12) and registered at the National Register (N°DRKS00005800). The recruitment period was from April to August 2014.

Patients between 18 and 60 years of age who provided written informed consent, were classified as American Society of Anesthesiologists (ASA) status I or II, and were undergoing elective surgery under general anesthesia were enrolled. The exclusion criteria were maintenance of anesthesia for < 60 min, existing contraindications for midazolam, propofol, sevoflurane, or rocuronium, and pregnancy. The following biometric data were collected: patient weight, height, age, sex, and ASA status.

Premedication and induction and maintenance of anesthesia were identical in each group according to the study protocol and corresponded to standard operating procedures of the Department. For all anesthetics, we utilized the same anesthesia machine (Aisys®, GE- Healthcare, Chalfont St Giles/Buckinghamshire/UK).

General anesthesia was administered by three appointed anesthesiology trainees with identical levels of professional experience (second year of residency). They were randomly allocated by blinded drawing selection, resulting in the assignment of operation rooms and the anesthesia technique. Each of the investigated anesthetists performed a minimum number of 10 for each technique, automatic end-tidal control.
(ETC. group) and manually controlled minimal flow (MC-MF group) anesthesia technique.

All patients received premedication consisting of midazolam (7.5 mg per os) and were pre-oxygenated with 100% inspiratory oxygen via a respiratory mask with a flow-rate of 10 l/min over 3 min. Standard hemodynamic monitoring included oscillometric measurement of blood pressure every 3 min and continuous 5-lead ECG and pulse-oximetry. General anesthesia was induced with 1 l/g/kg remifentanil and 2 mg/kg propofol. After administration of 0.6 mg/kg vecuronium, endotracheal intubation was performed. The inspiratory oxygen-fraction was maintained at 100%, and propofol was continuously administered at 4 mg/kg/h until the patient was transferred from the induction room to the operating room. Volatile anesthetics were started after connecting the patient to the ventilator in the operation room. The maintenance of anesthesia was performed with sevoflurane at a determined end-tidal concentration range of 1.2–1.4% and modified by dynamically adjusting the remifentanil infusion (0.2–0.8 l/g/kg/min). The investigated anesthetist chose the ventilation mode and adjusted ventilator parameters such as tidal volume (6–8 ml/kg) and respiratory rate to maintain a range of end-tidal CO2 of 30–40 mmHg according to the standard departmental guidelines.

Measurements were started (t0) when the patient was connected to the ventilator, which was pre-set with an oxygen-fraction of 100% and a flow-rate of 3 l/min. The anesthetists were instructed to immediately start ETC. or MC-MF (both with a flow-rate of 0.5 l/min). ETC. was started by the anesthetists pushing the end-tidal control button. ETC. was pre-set with a flow-rate of 0.5 l/min; the anesthetists had to determine the desired end-tidal sevoflurane target between 1.2 and 1.4% and the end-tidal oxygen target of 35% only once.

The following guidelines to perform MC-MF-anesthesia were shared with the investigated anesthetists. They were informed about the aim of an optimal economic performance by conducting MC-MF-anesthesia with a flow-rate of 0.5 l/min. The anesthetists were instructed to adjust only the composition of the fresh gas flow (FGF), whereas changes in flow-rates were to be avoided. They were guided to change the inspiratory oxygen-fraction to decrease or increase the expiratory oxygen concentration to reach target values, e.g., in case of undershooting the goal of 35–40% end-tidal oxygen concentration, they were advised to increase the inspiratory oxygen-fraction. The anesthetists were also instructed to start by applying a high inspiratory sevoflurane concentration (fully open the vaporizer) to reach the target-concentration of end-tidal 1.2–1.4% instead of increasing the FGF to wash-in sevoflurane.

The number of adjustments of the inspiratory oxygen-fraction and changes in the vaporizer setting, as performed by the anesthetists to reach and maintain target values, were recorded in the protocol as manual regulations, and counted by the investigators (who were continuously present in the operating room).

The first 60 min of anesthesia results were recorded and then divided into five time intervals for analyses:
- t0–5 min
- t5–10 min
- t10–15 min
- t15–30 min
- t30–60 min

The following endpoints were analyzed:

Primary outcome parameters:
- Number of adjustments needed to remain in the target range

Secondary outcome parameters:
- Time needed to reach a target-concentration of 1.2–1.4% end-tidal sevoflurane
- Time needed to reach a target-concentration of 35–40% end-tidal O2
- Consumption of sevoflurane (ml/kgBW/min)
- FGF of O2 (ml/min)

The data acquisition was performed by four anesthetists. Aside from FGF settings, the data were recorded from an integrated interface of the anesthesia machine and collected using the S5 collect program (GE Datex-Ohmeda, Helsinki, Finland). The data for the set FGF composition, and continuously displayed on the monitor, were documented manually every 10 s according to the study protocol. End-tidal oxygen and end-tidal sevoflurane data were continuously recorded by the software every 5 s. When
analyzing the data, all sevoflurane data outside the target range of 1.2–1.4% and all expiratory oxygen data outside the range of 35–40% were marked. We then determined the deviation by calculating the duration of missed target values separately for each time interval. Then, we calculated the percentage of the duration of missed targets in relation to the total duration of each time interval. Precision, or stability, was defined as the duration of reached target values and was determined by the inverse value of deviation (100% minus the percentage of missed targets); e.g., 100% stability was gained when the target values were maintained during the complete time interval.

The consumption of sevoflurane was calculated from the weight difference of the vaporizer before and after anesthesia with the use of a precision scale and a weight density of 1.5225 mg/ml (manufacturer’s specifications at 20°C: 1.520–1.525 mg/ml).

Statistics
The baseline characteristics of the patients were described using the median (25th and 75th percentiles) calculated for continuous variables (because all of the data were non-normally distributed according to Shapiro–Wilk tests) and the number (percentage) for categorical variables.

The determined minimal required sample per group was 29, calculated with the estimated precision of maintenance of anesthesia of 96% with the ETC. technique vs. 70% using MC-MF. On the basis of clinical experience, we estimated a 96% precision of maintenance of anesthesia with end-tidal control and a 70% precision of anesthesia using manually controlled minimal-flow anesthesia. We calculated a required sample size for the comparison of a proportion with a given proportion. The type I error—alpha was set at 0.05, and the type II error—beta was set at 0.01, which resulted in a minimal required sample size of 29 patients per group. Consequently, we planned a minimum of 30 patients per group.

The analyses were performed using MedCalc (Version 12.4.0, MedCalc-Software-bvba, Ostende, Belgium) and Statistica (Version 10, StatSoft-Inc., Tulsa/OK/USA) and included sample size calculation, testing of the distribution with the Mann–Whitney U-test (distribution of all continuous variables) or Chi-square test (distribution of sex and ASA-classification). Significance testing was two-sided with a significance level of 0.05. A P < 0.05 was considered statistically significant.

Results
We included 64 patients undergoing elective surgery under general anesthesia. The patients underwent the following types of surgery: maxillofacial surgery, ear, nose and throat surgery, gynaecological, trauma, orthopedic and plastic surgery. The study population consisted of 59% male patients with a median age of 40 years [interquartile range (IQR) 27–49]. The median body weight was 78 kg (IQR 69–88); the median height was 175 cm (IQR 168–183). Most of the patients were classified as ASA I (73%; Table 1). There were no significant differences in terms of biometric data between the two groups.

The group that underwent ETC.-anesthesia consisted of 30 patients; the group that underwent MC-MF-anesthesia consisted of 34 patients.

The use of ETC. led to a more precise maintenance of the sevoflurane target in all time windows (Fig. 1, Table 2): during the first 15 min 28% vs. 51% deviation from sevoflurane target, and from 15 to 60 min 1% vs. 19%, P < 0.0001.

Table 1 Biometric data.

<table>
<thead>
<tr>
<th></th>
<th>ETC.</th>
<th>MC-MF</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age [years: median (IQR)]</td>
<td>41 (30–49)</td>
<td>36 (24–49)</td>
<td>0.5312</td>
</tr>
<tr>
<td>Weight [kg: median (IQR)]</td>
<td>79 (68–86)</td>
<td>78 (70–90)</td>
<td>0.9893</td>
</tr>
<tr>
<td>Height [cm: median (IQR)]</td>
<td>174 (167–183)</td>
<td>175 (168–183)</td>
<td>0.9570</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>16 (53.3)</td>
<td>22 (64.7)</td>
<td>0.3553</td>
</tr>
<tr>
<td>ASA I [n (%)]</td>
<td>20 (66.7)</td>
<td>27 (79.4)</td>
<td>0.2493</td>
</tr>
</tbody>
</table>

No significant differences between the ETC.-group and the MC-MF-group were found. ETC., end-tidal control; MC-MF, manually controlled-minimal-flow; BW, body weight.
manual adjustments were needed in the ETC.-group once ETC. was started \((P < 0.0001)\).

Expiratory O_2 deviated significantly less from the target range using the ETC. technique in the first 30 min \((t0–15\) min: 45% vs. 86% deviation from O_2 target, \(P < 0.0001\); \(t15–30\) min: 3% vs. 26%, \(P = 0.005\)). However, from 30 to 60 min, no improvement in precision was observed in the ETC.-group compared with the MC-MF-group \((P = 0.197)\) (Fig. 2). Manual control of O_2 FGF required a maximum of 11 changes within 60 min of anesthesia time, and a median of five (IQR 3–6) changes was recorded, whereas in the ETC.-group, similar to the regulation of the sevoflurane concentration, no manual changes were needed once the target was set when starting the automatic ETC. \((P < 0.0001)\).

The time required until the end-tidal target-concentration of sevoflurane was longer in the MC-MF-group \((P < 0.0001)\). In the ETC.-group, 178 s elapsed, while in the MC-MF-group, 275 s elapsed before the end-tidal concentration of sevoflurane was in the target range of 1.2–1.4%. Using ETC., a higher consumption of sevoflurane was observed \((P = 0.0044)\): 1.5 vs. 1.3 ml/kg/min*1000 or 6.9 vs. 6.0 ml/h, respectively \((P = 0.0004); Table 2\). One patient in the ETC.-group and one patient in the MC-MF-group were missing data pertaining to the sevoflurane vaporizer weight and therefore were excluded from the analysis of sevoflurane consumption.

The median time period until expiratory O_2 was \(\geq 35\) and \(\leq 40\%\) was shorter \((P < 0.0001)\) in the ETC.-group (232 s vs. 764 s), while the O_2 flow was significantly higher in the ETC.-group in the first 15 min. From 15 min onwards, the O_2 flow was approximately identical in both groups (Table 3).

**Discussion**

We found that target-concentrations of sevoflurane and oxygen were more stable with the use
of ETC. compared with MC-MF-anesthesia. The MC-MF technique required numerous interventions to maintain the defined target ranges. From 15 to 30 min, the targets were missed approximately 25% of the time. From 30 to 60 min, no deviation in the median was found with regard to the expiratory oxygen target, but the sevoflurane target was missed 11% of the time.

The target-concentrations of end-tidal oxygen and sevoflurane were reached earlier with the ETC. technique. With the ETC. technique, the initial reduction to a desired expiratory oxygen concentration of 35–40% was achieved by automatic short switching to an increased FGF to wash oxygen out, which initially resulted in a higher FGF and consequently in a higher total sevoflurane consumption of 6.9 (ETC.) vs. 6.0 ml/h (MC-MF). It is possible that the difference in sevoflurane consumption might diminish with longer anesthesia time windows of 120 or 180 min. Changes in fresh gas composition and desired volatile anesthetic concentrations demonstrate delayed effects in constant MF techniques when the FGF is not increased to wash out oxygen. This explains the longer time required with the manual technique to reach the sevoflurane target and the expiratory oxygen concentration of 35–40% following the 100% inspiratory oxygen-fraction during induction.

In our study, using ETC., the sevoflurane target was reached only 33 s later (although our target-concentration was set higher) than reported in a study by Lucangelo using a fresh gas flow of 1 l/min with the same equipment as we did. They reported 137 necessary adjustments of the vaporizer for 40 patients; in our study, a median of eight adjustments were needed to reach and maintain precise sevoflurane targets over a total 60 min of anesthesia time. Compared with our findings, Lucangelo observed slightly lower sevoflurane consumption using ETC. than we did (0.11 vs. 0.12 ml/min) but higher consumption using MC anesthesia (0.12 vs. 0.10 ml/min). Since the authors did not set targets for the maintenance of sevoflurane concentration but rather modified the targets according to patient requirements, the comparison remains limited.

In a study using anesthesia machines in vitro (FGF 1 l/min), sevoflurane targets of 0.9% MAC were reached more rapidly for both the automatic and manual techniques compared with our results. The stability of 0.9 ± 0.1% MAC from 7 to 15 min was identical to our results from 10 to 15 min. With the MC-MF technique, we recorded a higher stability of 91% during the 10–15 min time period (vs. 80% and 45%). Lortat-Jacob found no difference between the two techniques in terms of the time needed to reach the target-concentration of desflurane using a FGF of 1 l/min.

DeCooman et al. also observed higher anesthetic consumption with the ETC. technique than the MC-MF technique, as we did, which was caused by the use of a high FGF for the initial circuit and lung wash-in, suggesting optimization of the algorithms that manage the initial FGF. This result indicates that reduced consumption is only possible when minimizing the FGF in both the ETC. and MC-MF techniques.

Our findings indicating the high percentage of missed targets and the high number of adjustments with MC anesthesia show that MC-MF-anesthesia requires the constant focused attention of the anesthetist and remains a difficult task. We agree with the results of previous studies stating that automatic ETC. systems allow for more stable and more accurate target-concentrations that are achieved more quickly than under human control. Considering that the participating anesthetists were engaged at a maximal level of attention within this study.

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**Table 3 Oxygen flow in each time window.**

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<th>ETC.</th>
<th>MC-MF</th>
<th>P</th>
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<tbody>
<tr>
<td>t0–5 [ml/min: median IQR]</td>
<td>1141 (899–1380)</td>
<td>533 (300–1033)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>t5–10 [ml/min: median IQR]</td>
<td>235 (197–292)</td>
<td>45 (0–154)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>t10–15 [ml/min: median IQR]</td>
<td>327 (289–349)</td>
<td>113 (50–162)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>t15–30 [ml/min: median IQR]</td>
<td>296 (272–314)</td>
<td>299 (244–317)</td>
<td>0.9410</td>
</tr>
<tr>
<td>t30–60 [ml/min: median IQR]</td>
<td>301 (283–315)</td>
<td>295 (276–319)</td>
<td>0.7724</td>
</tr>
</tbody>
</table>

The O2 flow [ml/min] was higher in the ETC.-group in the first 15 min due to an initial wash-in period (P values < 0.05 are marked in bold). From 15 min onwards, the O2 flow was approximately identical in both groups. ETC., end-tidal control; MC-MF, manually controlled-minimal-flow.
setting (while continuously being observed by the investigating anesthetists), known as the Hawthorne effect, the percentage of missed targets may be regarded as a concerning finding. Missing the threshold of sevoflurane concentration, not only by surpassing it but also by falling beneath it, carries the potential for insufficient depth of anesthesia, which is, in addition to accidental hypoxia, a potential risk of MC anesthesia. Sieber and colleagues stated that the clinical significance of the AC technique lies in the more reliable avoidance of minimal and maximal values of the control variable and could therefore contribute to a lower risk of awareness. However, we did not observe hypoxic gas mixtures or inappropriate low anesthesia levels at any time in both study groups.

We demonstrated that automatic ETC. can facilitate MF-anesthesia with a clinically more acceptable workload, whereas the MC-MF technique involves constant adjustments of the gas composition and vaporizer settings and thereby occupies the workforce and their attention. Today’s anesthetists are confronted with finding a balance between the conflicting goals of rapid adjustments to gas concentrations and reducing the consumption of volatile anesthetics by minimizing the FGF. We observed that ETC. helps to provide a ‘controlled’ experience with MF-anesthesia in everyday practice and can promote and establish the safe and reliable use of MF. Accordingly, ETC. will further enhance the feasibility of MF techniques, and median flows in the range from 0.5 to 1.0 l/min may then be realistically achievable targets. ETC. may in fact increase in the use of low-flow anesthesia due to its economic and environmental benefits while simplifying the process of anesthesia by reducing the number of required interventions.

We can state that the advantage of ETC. primarily lies in the stable and reliable maintenance of target-concentrations compared with MC-MF-anesthesia, which, as we showed, required numerous manual adjustments, and thereby requires substantial attention of the anesthetists. Consequently, ETC. reliably contributes to precise anesthesia and can support and release anesthetists, in the context of increased performance density under changing conditions by the ongoing development of technical work stations. Kennedy et al. reported that anesthetists valued workload reduction after the introduction of automated agent delivery with ETC. In particular, with a decreasing number of experienced consultants and an increasing number of younger residents, supporting resources such as ETC. will play a greater role.

Limitations of the study
To obtain a comparable setting between the two anesthesia techniques, we chose to analyze anesthesia conducted by the same three anesthetists (each performing a minimum number of 10 for each technique). This small number of participating anesthetists may be regarded as a limitation of the study. Furthermore, analyzing anesthetists with 1 year of experience may have influenced our results. However, in our department, MF is the standard technique and is mandatory for all anesthetists, allowing young anesthetists to become familiar and experienced with the challenge of MF-anesthesia. But being aware of the fact that MF requires experience and insight, the participating anesthetists were given additional training in MF-anesthesia ahead of the study to ensure that they had already gained routine experience. Indeed, in the clinical routine, we observed no difference in the quality of MF-anesthesia performance between young and experienced residents.

Moreover, the daily assignment of study patients to the three anesthetists was not randomized but was performed by daily management depending on the conditions in the operating theatres, available anesthesia machines and individual schedules, thus explaining the study period duration of 5 months.

In many places, there is no induction room as in our study settings and anesthesia is induced in the operation room. However, ETC. and MC-MF are both techniques that are not used during induction of anesthesia, but during maintenance. Since we recorded and analyzed anesthesia after induction, beginning with the use of sevoflurane, our findings can be generalizable to any anesthesia maintained with volatile anesthetics.

Conclusion
In our prospective, comparative study, we found that target-concentrations were maintained at...
more stable levels with the use of ETC., while MC-MF-anesthesia required numerous interventions to maintain the defined target ranges of sevoflurane and end-tidal oxygen concentration. The target-concentrations were reached earlier with the use of ETC. compared with MC-MF-anesthesia, but at the expense of a slightly greater use of anesthetic agents. Our findings led to the conclusion that ETC. contributes to precise and secure anesthesia and is an effective technique that supports the anesthetist.

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