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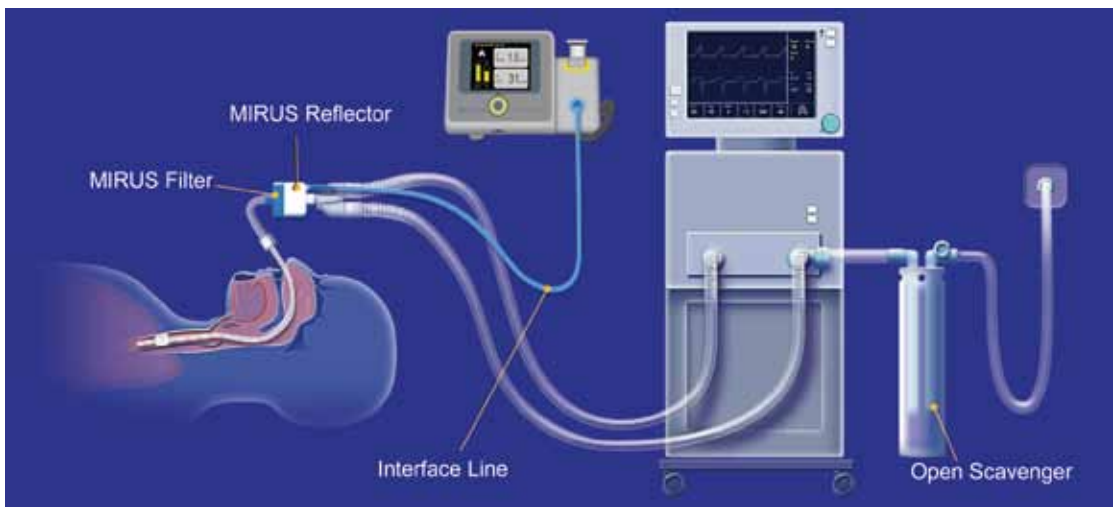
Volatile anaesthetics in intensive care

Target level controlled automatic sedation using the MIRUS™ System

Analgosedation of mechanically ventilated patients in intensive care units calls increasingly for concepts that permit early (predictable) weaning and rapid extubation. The aim is to achieve the greatest degree of cognitive recovery and early mobilisation. Ideally, patients should be able to breathe spontaneously under sedation, while remaining pain-free, alert and cooperative. Intravenous sedation used in the everyday routines of intensive care units is largely unsuitable to achieve these goals. Mentioned in the S3 Guideline on the Management of Analgesia, Sedation and Delirium in Intensive Care Medicine, the use of volatile anaesthetics (VA) presents a possible alternative.[1]



Volatile anaesthetics are becoming increasingly interesting as a means of sedating mechanically ventilated patients in intensive care units, as they possess properties that can contribute to weaning the patient from mechanical ventilation as quickly as possible.

Among the reasons for this is that the end-tidal concentration of VA administered (etVA) provides a measurable and controllable parameter for the depth of sedation otherwise unavailable with intravenous sedation. Here it has been demonstrated that the measured etVA levels correlate significantly with the blood gas concentration of VA and its concentration in the brain, as well as with the RASS (Richmond Agitation Sedation Scale) score.[2] By exploiting this correlation, modern application systems use etVA measurement to enable individual control of the target level as required in each instance. A system of this kind, MIRUS™, has been available on the market since 2015.

etVA: measurement and control parameter for sedation depth

In a simplified sense, the MIRUS System adjusts sedation like the cruise control feature in motorised vehicles. This is based on the continuous, non-invasive measurement of etVA concentration using a gas monitor integrated in the MIRUS controller. The first step is to enter the necessary target MAC; the concentration of anaesthetic gas is then compared with the etVA measurement and adjusted automatically. At the heart of this process is the MAC pilot. It continuously calculates the difference between etVA/MAC and target MAC, and also considers the gas volume returned from the MIRUS reflector positioned close to the patient. This guarantees that only the required amount of anaesthetic gas is administered at any time. The system also registers alterations in the patient's spontaneous breathing, as well as changes in the configured mechanical ventilation parameters or fluctuations in myocardial perfusion. The system responds by adjusting the administration of the active substance to maintain the MAC target level. The MIRUS System is compatible with all standard anaesthetic gases. Like vaporiser systems used in anaesthetics, the MIRUS controller is also available in variants for specific substances like isoflurane, sevoflurane and desflurane.

Practical application has shown that the desired sedation depth, for instance a RASS of -2, is achieved reliably and can be maintained for the majority of patients after configuring MAC of 0.5. Clinical experience acquired so far has indicated that intensive care patients require significantly higher levels of around 1 MAC in exceptional cases only. Nevertheless, the MIRUS System has no difficulty achieving these levels in the shortest time. Overall, the extremely rapid onset and offset of the VA enables the achievement of all sedation depths in a tightly controllable setting without co-sedation, while also keeping opiate requirements at a low level. Moreover, spontaneous breathing can be maintained even during deep sedation (RASS -5), as inhalation sedation using VA does not significantly affect the patient's breathing patterns. Therefore, the principal advantages of inhalation sedation concepts include the option for early weaning of the patients and rapid extubation. A spontaneous breathing test can be performed at RASS scores of between -1 and -3. The respiratory depression caused by opiates allows an adequate adjustment of sedation depth for mechanically ventilated patients in this situation. A spontaneous breathing frequency above 20 min^{-1} indicates that the analgesic administered to the patient is too low, which is corrected by increasing the opiate dose. Breathing frequencies below 10 min^{-1} suggest that the dose is too high and can be reduced accordingly. Sedated patients receiving adequate analgesic will usually breathe with a frequency of 10–20 min^{-1}. The MIRUS System maintains the defined sedation, even for patients with occasionally irregular breathing patterns receiving assistant spontaneous breathing, enabling a direct control, i.e. monitoring, of this factor and the analgesic depth as two of the eminently crucial parameters for patient outcome. Beyond medically induced, deep sedation or analgesia, it should therefore become possible to provide patients with scheduled and measurable analgesic doses that are adjusted to their specific situation.

Target level controlled sedation with VA: when should it be indicated?

VA administered by inhalation leaves the patient's body via the breathing respiratory tract. An essentially inert substance, an almost negligible percentage (0.1, i.e. 0.01% iso- and desflurane) is metabolised, hence preventing the release of toxic metabolites. A metabolisation rate of 4% must be considered for sevoflurane, which is noticeable above all in the elevated plasma level on fluoride ions.

Compared to intravenous sedation, inhalation sedation hence has the advantage that it does not present a further risk to patients with liver or kidney damage caused by the breakdown of the sedative, i.e. accumulation of the sedative or its metabolites. Eliminated quickly, VA are also associated with shorter wake-up times, faster cognitive recovery and improved predictability of wake-up times, as demonstrated in postoperative examinations following short-term sedation with desflurane vs. propofol and elsewhere.[3]

Instructions contained in the S3 Guideline indicate and justify the selection of this option based on the requirement for short wake-up times and the restoration of cognitive functions, as well as the need for rapid mobilisation.[1] The recently published eCash concept (= *early Comfort using Analgesia, minimal Sedatives and maximal Humane care*)[4] also advocates the lowest possible level of sedation for intensive care patients. This patient-centric procedure attaches the highest priority to flexible, multimodal analgesia with a strict limitation of opioid use. It also emphasises that the procedure applied to – clinically necessary – sedation is significant, as it largely determines the ability to preserve spontaneous breathing and initiate early weaning. In a recent publication, the American Thoracic Society (ATS) recommended that sedation and weaning should always be considered as closely related issues and that protocols to minimise sedation must be brought to the fore.[5]

Indications of a better outcome

Randomised controlled trials and prospective cohort studies suggest that the applied sedation concept can influence the outcome for mechanically ventilated intensive care patients.[6] For instance, long-term studies have yielded indications that daily interruption of sedation, in connection with spontaneous breathing tests, has a significantly favourable effect on the 360-day survival of patients. Another

investigation concluded that the 180-day survival rate following light sedation and the reduced administration of benzodiazepines in particular (e.g. midazolam) was significantly better than after conventional application of these substances. A current retrospective study at Katholisches Klinikum Bochum of 200 long-term sedated patients with complex or prolonged weaning also provided evidence for significant effects on hard outcome parameters. A comparison of patient groups sedated using VA (isoflurane) with those receiving midazolam/propofol revealed significant differences in clinic mortality ($p < 0.005$) and 360-day mortality ($p < 0.013$). There was also a significantly higher discharge rate of 60 % vs 37 % for patients sedated intravenously after approximately 3 months hospital treatment. This variance also remained significant after one year. [7] Observations demonstrating the statistical likelihood that only 5 patients need to be treated with VA in order to prevent one fatality, underline the procedure's potential clinical relevance.

Ambient air contamination with VA

It is always essential to consider the exposure of hospital staff to trace concentrations of anaesthetic gas in the context of administering VA in intensive care units. Indeed, questions were asked many years ago as to the toxic side-effects for employees, and substantial uncertainty persists even today in some areas.

It is true that the data situation from modern VA is limited, the findings are contradictory, and the transferability of results into clinical practice is often difficult due to methodical problems (including additive exposure to X-ray, alcohols, comparison with anaesthetic gas mixtures). Overall, however, the majority of studies indicate that a chronic exposure to low concentrations (< 2 ppm) of isoflurane, sevoflurane and desflurane do not lead to organic dysfunction, cognitive impairment or reduced fertility[8–10]. Indications of a teratogenic effect of desflurane and sevoflurane on the human organism are not documented, although there are records of an approximately 10 % reduction in the birth weight of litters born to rats after exposure to desflurane, as well as organic abnormalities in the progeny of mice exposed to high concentrations of sevoflurane during gestation. Retrospectively collected indications of an elevated risk of miscarriage and deformation among the children of employees exposed to isoflurane during pregnancy were not confirmed in a prospective study conducted at a later date[11–15]. In regard to a possible genotoxic effect after exposure to all 3 VA, there were indications for an elevated rate of sister chromatid exchange, but no evidence of increased structural chromosome aberration. It is questionable whether an actual risk for downstream pathological conditions among staff members can be inferred on this basis[16–24].

In summary, the risk of harmful effects due to low-dose, long-term exposure to isoflurane, sevoflurane and desflurane is likely very small, although it cannot be excluded entirely. Accordingly, there are no universally valid, workplace limit values for these substances. Some countries have already defined limit values, but they differ substantially in some cases and cannot be justified in this form based solely on currently available literature (e.g. 10 ppm in Austria and Switzerland for isoflurane, but 50 ppm in England). Suitable limit values are still pending in Germany (Committee on Hazardous Substances (AGS) review list / UA III on TRGS 900 and TRGS 910; valid: Nov. 2016).

MIRUS System: moderate exposure with VA < 1 ppm

It was therefore interesting to investigate from the perspective of application safety the extent to which personnel working in an intensive care unit would be exposed to VA during operation of the MIRUS System. It is important to note first of all that the VA exhaled by the patient is largely retained by the MIRUS reflector and then added to the next inspiration of ventilation gases. Any residual fractions of VA that enter the expiration are disposed of directly at the expiration outlet via an open reservoir scavenger system (ORS) connected to the vacuum system.

Photoacoustic gas measurement was used to determine exposure to VA and conducted at Katholisches Klinikum Bochum. This has been an established method for years and is considered extremely sensitive with a lower detection limit for VA of 0.01 ppm. Moreover, it enables real-time measurements incorporated in clinical routines. All measurements were conducted in air-conditioned patient rooms with fitted systems for VA extraction and disposal. In total, 5 one-hour measurements of ambient air concentration revealed a moderate exposure of < 1 ppm at 4 of the defined measurement positions. A significant variance between the gases was not observed. The highest measured levels of 0.6 ppm were recorded at a distance of 0.25 cm above the tracheostoma/tube, i.e. at a distance of 20 cm from the anaesthetic gas extraction system. An ambient air contamination of < 0.5 ppm was measured at the centre of the room, within the anticipated inhalation range of the personnel (1.5 m above the floor).

Additional long-term measurements demonstrated the incidence of elevated measurement levels replenishing the VA in particular. A VA-specific adapter with a valve system to prevent leakage is used to refill the reservoir in the MIRUS controller directly from the bottle. Nevertheless, there may be tiny splashes of VA when detaching the bottle. It is therefore important to take sufficient time to complete the steps associated with replenishing the reservoir. Unintentional opening of the ventilation system during active operation is also a theoretical source of exposure to VA. The MIRUS System is fitted with a disconnect alarm to alert the personnel of this situation; it also automatically discontinues administration of anaesthetic gas. Application does not continue until clinical pressure and flow conditions have been restored. Comparative measurements with and without the anaesthetic gas extraction and disposal process installed for the MIRUS System proved its effectiveness to minimise ambient air contamination.

Considerations for use from a nursing perspective

Experience obtained from clinical practice suggest that the MIRUS System can be easily integrated within intensive care routines. Also, it has been demonstrated that the time required to connect the system and to perform a self-test is no longer than is needed to prepare intravenous sedation. The specialist nursing staff has signalled that operating the monitor unit is comparatively simple and intuitive. There are various potential benefits associated with using the system in a nursing context, compared to intravenous sedation. One of them refers to hygiene, i.e. existing infection risks, as operation of the VA requires less manipulation of the central, intravenous access. Moreover, the discontinuation of sedatives applied intravenously also reduces the risk of the frequent incompatibilities between the numerous medications administered concomitantly in intensive care units. Automated sedation control can substantially reduce the time required for follow-up monitoring otherwise needed for intravenously applied sedatives as well. Experience acquired so far indicates that use of the method in treatment routines appears particularly sensible if there are early indications of problems in the mechanical ventilation of certain patients. They include patients with an anticipated ventilation period of more than 48 hours, patients with prior impairments in organ functions or multi-morbidity, as well as patients who are difficult to sedate. The bronchodilatory effect of VA can lead to a rapid improvement in the acute condition of patients suffering from chronic obstructive pulmonary disease, i.e. asthma.

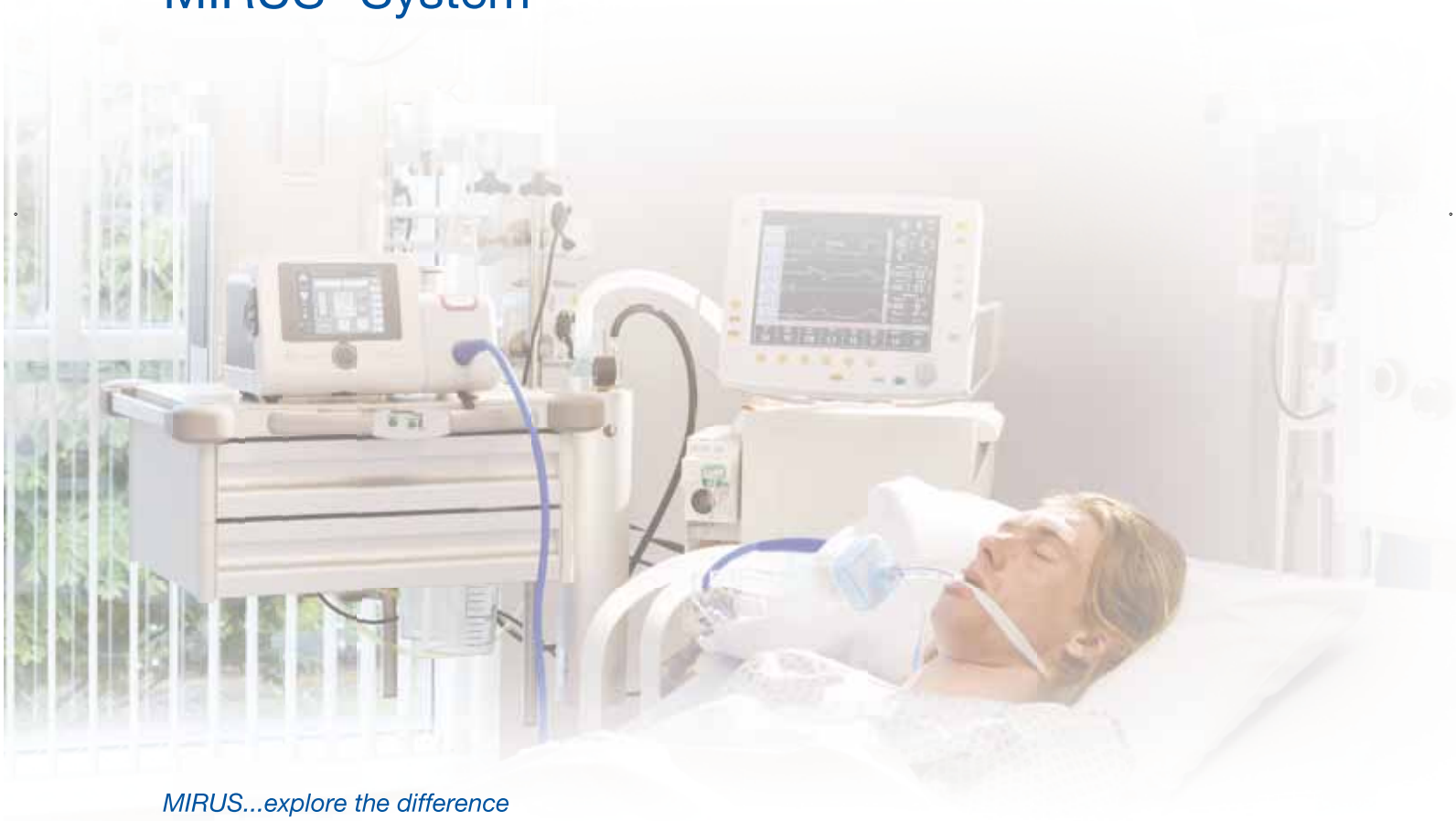
Conclusions for clinical practice

- Sedation with VA is an attractive alternative to concepts for the intravenous administration of substances. Indications can be defined based on the criteria set forth in the S3 Guideline.
- Combined with the VA substance properties, modern application systems based on etVA measurement enable individual target level control for the required sedation depth.
- The outstanding controllability produces extremely short wake-up times and a rapid neurological assessment of the patient.
- The requirement of the S3 Guideline, namely that the patient must be essentially pain-free, alert and cooperative under sedation, can be implemented overall using an inhalation-based concept.
- Spontaneous breathing can be preserved during inhalation sedation, enabling rapid weaning of the patient from mechanical ventilation, as well as extubation.
- Data collected retrospectively in regard to patients who received long-term mechanical ventilation indicate a lower rate of hospital mortality and 360-day mortality.
- There is no clear evidence of a harmful effect of VA following chronic low-dose, long-term exposure, although it cannot be excluded entirely.
- There are currently no valid regulations for VA workplace limit values in Germany. Measurements of ambient air contamination during use of the MIRUS system revealed low findings < 1 ppm.
- Experience from everyday clinical practice has shown that the MIRUS System can be easily incorporated in intensive care (nursing) routines.

Source: Industry Symposium during the Bremen Intensive Care Congress on 15/2/2017

MIRUS

Volatile anaesthetics in intensive care: **Target level controlled** sedation using the MIRUS™ System



MIRUS...explore the difference

Speakers:
Dr Michael Tübben D.E.S.A. (Korbach)
Senior Consultant for Anaesthesia and Surgical Intensive Care, Stadtkrankenhaus Korbach

- What are the objectives, and how can VA contribute?

Dr Martin Bellgardt (Bochum)
Director and Consultant for Intensive Care at the Clinic for Anaesthesiology and Surgical Intensive Care, Katholisches Klinikum Bochum, University Hospitals of the Ruhr University of Bochum

- Target: the earliest possible weaning and extubation

Dr Jenny Herzog-Niescery (Bochum)
Katholisches Klinikum Bochum, University Clinic for Anaesthesiology and Surgical Intensive Care

- Anaesthetic gas contamination of the ambient air: To what extent is the personnel at risk?

Monika Tielmann (Andernach)
Specialist nurse for Alice anaesthesia/intensive care and breathing therapist

- Practical administration of inhalation sedation using the MIRUS System

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