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ARTICLE TYPE

Trap-and-release membrane inlet ion mobility spectrometry for on-line measurement of trace propofol in exhaled air

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Monitoring the exhaled propofol concentration is helpful for anaesthetists to ensure the safety of patients and to adjust the anaesthesia depth. In this study, a trap-and-release membrane inlet ion mobility spectrometer (TRMI-IMS) was constructed for on-line measurement of trace propofol in exhaled air. The effects of trap-and-release parameters such as trap temperature, release temperature and carrier gas flow rate were investigated. Once optimum experimental parameters were identified, the limits of detection (LODs) for propofol at sampling times of 0.5, 1, 2, and 3 min were found to be 17, 8, 3, and 2 pptv, respectively. With a sampling time of 1 min, the response of TRMI-IMS to propofol was enhanced by a factor of 9 as compared with that of constant temperature MI-IMS; the calibration curve resulting from three individual experiments was linear in the range of 0.1 to 2.5 ppbv. Finally, TRMI-IMS was performed on eleven patients undergoing thyroidectomy surgery to on-line monitor the exhaled propofol. The correlation coefficients (R^2) between TRMI-IMS signal intensities and calculated propofol plasma concentrations set in TCI system were estimated to be in a range of 0.69 to 0.93, demonstrating the potentials of TRMI-IMS for on-line predicting the propofol concentration in plasma by exhaled air analysis.

Introduction

Propofol is a widely used intravenous anaesthetic. So monitoring propofol concentrations during surgery is important to ensure the adequate anaesthesia for patients. However, suffering from the pretreatment of blood samples, the measurement of propofol concentration in plasma is usually off-line and time-consuming. Fortunately, the propofol concentration in plasma was found to be related with that in exhaled air,¹⁻³ opening a new avenue for non-invasively estimating its plasma level by exhaled air analysis. In recent years, much attention has been given to mass spectrometric measurements of the exhaled propofol.¹⁻¹¹ Among these, Takita⁴ et al. and Harrison¹ et al. carried out a feasibility trial to continuously measure the propofol in exhaled air by proton transfer reaction mass spectrometry (PTR-MS). Boshier⁵ et al. and Hornuss^{6,8} et al. completed the on-line monitoring of exhaled propofol in patients undergoing anesthesia over the total operating period by selected ion flow tube mass spectrometry (SIFT-MS) and ion-molecule reaction mass spectrometry (IMR-MS), respectively. Grossherr^{2,9} et al. quantified the exhaled propofol using propofol adsorption by Tenax-TA and subsequent thermal desorption, followed by the measurement via gas chromatography mass spectrometry (GC-MS); in these studies, the exhaled propofol concentration was estimated in the ppbv range. Also, exhaled propofol has been detected by the techniques such as photoacoustic spectroscopy¹⁰ and optical

spectroscopy.¹¹

Recently, ion mobility spectrometry (IMS) emerged as another attractive method for the exhaled propofol measurement,¹²⁻¹⁴ featuring its high sensitivity, good portability, and atmospheric pressure operation. Perl and Carstens et al. combined IMS with a multicapillary column (MCC-IMS) to allow the isolation of humidity in the breath,^{12,13} overcoming the problem that a high humidity would reduce the selectivity and sensitivity of IMS.^{15,16} Kreuder et al. found that the sensitivity of MCC-IMS for propofol in the negative mode was higher as in the positive one.¹⁴ In our previous study,¹⁷ we constructed a constant temperature membrane inlet ion mobility spectrometer (CTMI-IMS) for on-line measurement of exhaled propofol, with a linear response range of 10-83 ppbv. Benefiting from the silicone membrane, the interference of humidity was almost eliminated and the selectivity of propofol was improved. Whereas, the exhaled propofol concentration in clinical setting is probably down to 1 ppbv,⁵ so in this case, CTMI-IMS is unable to accomplish the quantitative analysis.

The trap-and-release membrane inlet has been interfaced to mass spectrometer for the detection of volatile and semi-volatile organic compounds,¹⁸⁻²³ which is an effective method to improve the analytical sensitivity. Consequently, in this study, a stand-alone IMS in combination with a trap-and-release membrane inlet (TRMI-IMS) was built to improve the detection sensitivity of propofol to sub-ppbv level to meet the clinical requirements. In order to evaluate the capability of TRMI-IMS in real clinical

setting, it was tested on eleven patients undergoing thyroidectomy surgery to on-line measure the propofol in exhaled air.

Experimental

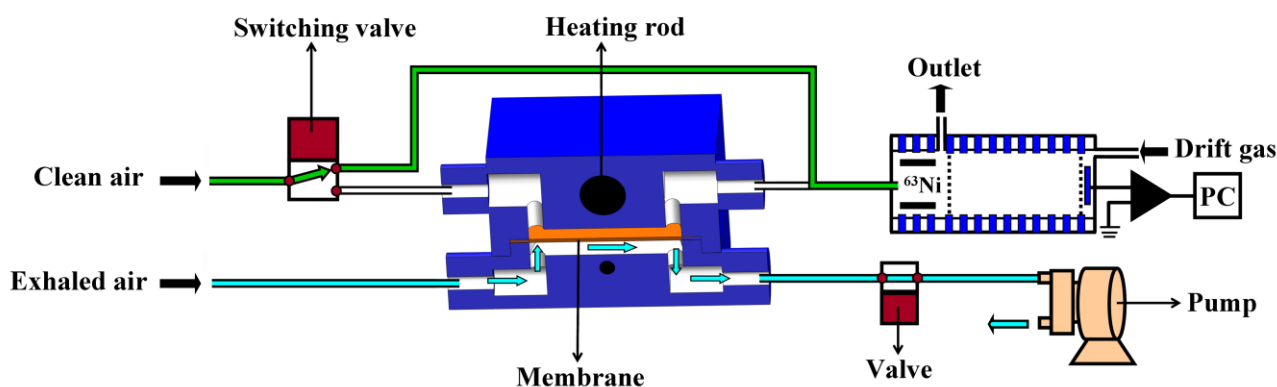
Apparatus

The schematic drawing of the TRMI-IMS apparatus is shown in Fig. 1, and the details of the ion mobility spectrometer have been described previously¹⁷. Under a lower membrane temperature, the sample gas was pumped through the feed side of the membrane for analytes to be trapped in it, while the carrier gas flow was introduced into the IMS directly, as shown in Fig. 1a. Then, the

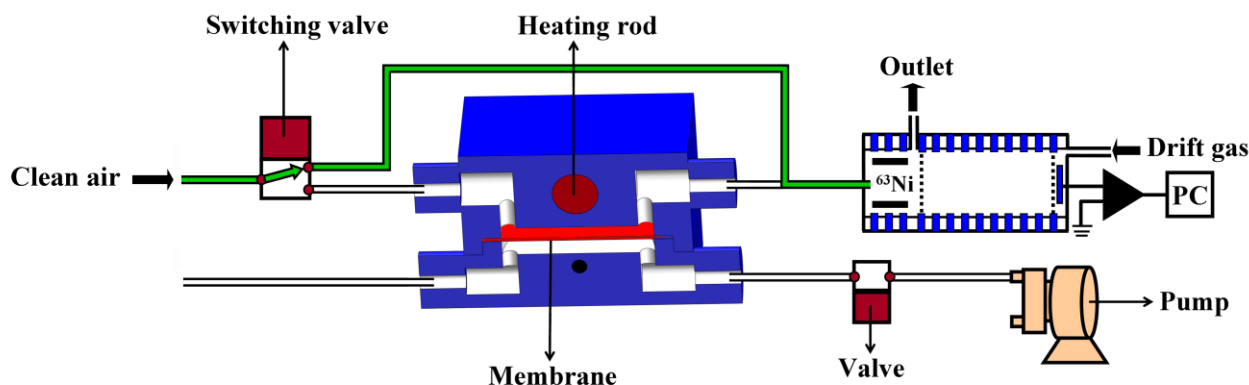
sample flow was cut off via a valve and the membrane temperature was increased rapidly, as shown in Fig. 1b. Finally, the carrier gas flow was switched into the permeate side of the membrane by a switching valve, followed by the injection of released analytes into the IMS, as shown in Fig. 1c. What is more, the membrane inlet here also can be operated in the constant temperature mode, and the procedure was the same as reported in ref. 17.

Clean air, purified and filtrated by silica gel, activated carbon, and 13X molecular sieve traps, was used for both the carrier gas and drift gas, and its moisture level was kept below 1 ppm. The flow rate for the carrier gas and drift gas was 300 and 500 mL/min, respectively. The IMS cell was operating at 90 °C.

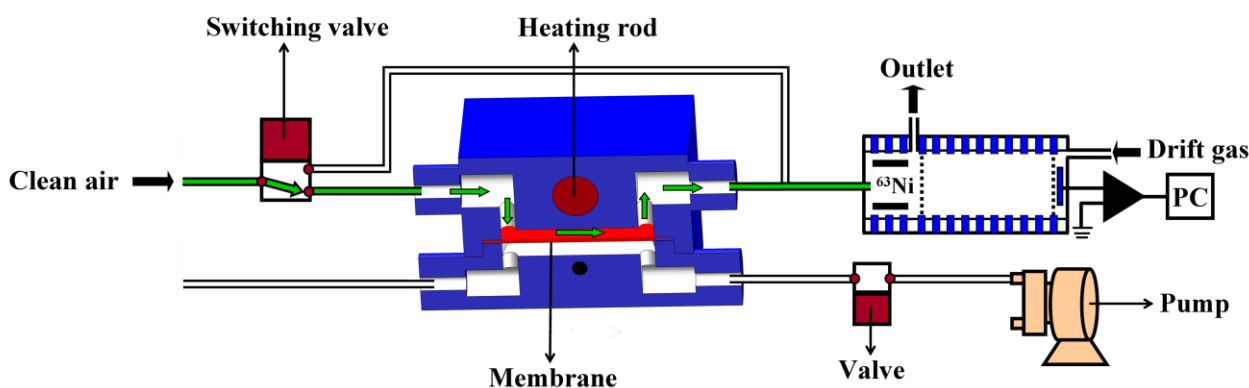
(a) Sampling process



(b) Desorption process



(c) Injection process



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Fig. 1 Schematic drawing of the trap-and-release membrane inlet ion mobility spectrometer (TRMI-IMS) apparatus in (a) sampling process, (b) desorption process and (c) injection process.

Sample gas preparation

Propofol was analytical grade and purchased from J&K Scientific Ltd. (Beijing, China). The gaseous propofol sample was obtained by permeating method, and the details is described as following: 1 mL pure liquid propofol was sealed in a 2 mL vessel; then its silicone cap was drilled with a fine sharp needle to allow the propofol gas to diffuse out; the propofol gas was immediately carried away by purified air at a constant flow rate; after a week, the mass loss of this vessel was weighed; at a constant temperature of 25 °C, its concentration of propofol was calculated to be 5 ppbv. Lower concentrations of propofol were made by further dilution of this mixture with clean air using two sets of flow controllers.

Results and discussion

Optimization of the trap-and-release parameters

To achieve the best sensitivity for propofol, the experimental parameters related to the membrane inlet, such as the trap temperature, release temperature, and carrier gas flow rate were optimized. In each measurement, after the injection of released propofol into the IMS, the propofol intensity exhibited the following temporal profile: It rose rapidly, achieved a maximal value (defined as I_{\max}), and then gradually decayed, as demonstrated in Fig. 2a. Here, the time required to decay by 50% maximal intensity is defined as $t_{1/2}$, which determines the analysis speed.

In Fig. 2b, the trap temperature was investigated from 30 to 70 °C. As expected, the lower trap temperature, the stronger I_{\max} , which can be ascribed to higher solubility of propofol in the membrane at lower membrane temperature. However, with a lower trap temperature, more time is needed for cooling the membrane before the subsequent measurement. Hence, by maintaining a compromise between the cooling time and I_{\max} , a trap temperature of 50 °C was chosen for the following experiments.

Fig. 2c displays the effects of release temperature on I_{\max} (maximal propofol signal intensity) and $t_{1/2}$ (the time required to decay by 50% maximal intensity). This Figure shows that I_{\max} initially increases and reaches a maximum at a release temperature of 160 °C; afterward, it decreases when the release temperature is further increased. The initial increase should be attributed to the more released propofol at higher release temperatures. Whereas, at the release temperatures higher than 160 °C, the decreasing intensity might be resulted from the released impurities from the membrane, giving rise to the competitive reaction between these compounds and propofol in IMS. Considering that the higher release temperature, the shorter $t_{1/2}$, an optimized release temperature of 160 °C was selected.

For TRMI-IMS, the carrier gas served to inject the released propofol into the ionization region. As depicted in Fig. 2d, an increasing flow rate from 150 to 250 mL/min brings an enhancement for I_{\max} , as a result of the higher injection efficiency of propofol from the membrane inlet into the IMS. Nevertheless, as the flow rate is further increased, decreasing I_{\max} is found, which is due to the dilution of propofol in the carrier gas.

Furthermore, a higher flow rate would result in a decrease of $t_{1/2}$, thus, taking account of both I_{\max} and $t_{1/2}$, the carrier gas flow rate was optimized as 300 mL/min.

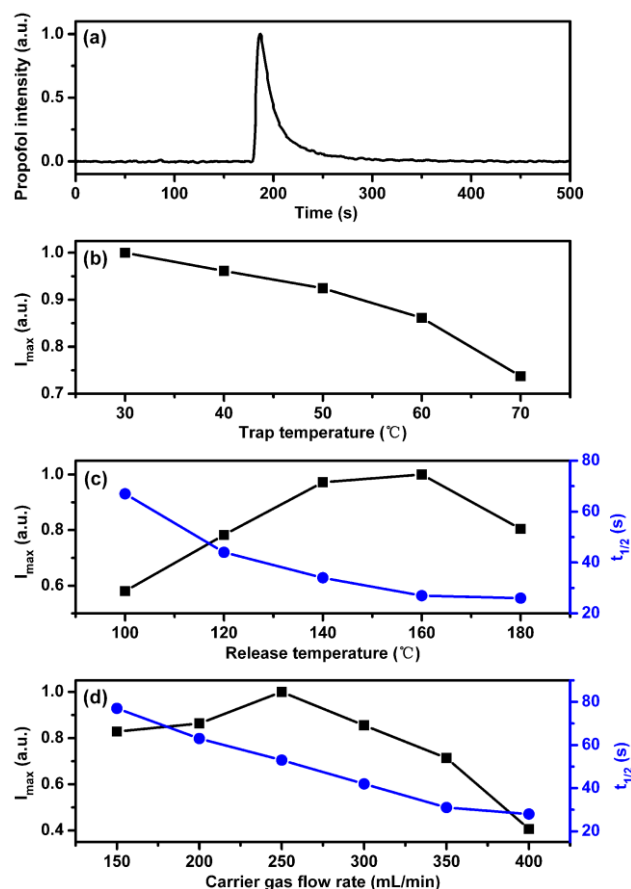


Fig. 2 (a) The temporal profile of the propofol peak intensity. Effects of (b) trap temperature, (c) release temperature, and (d) carrier gas flow rate on I_{\max} (black squares) and $t_{1/2}$ (blue dots). The release temperature in (b) was 140 °C and the trap temperature in (c) was 50 °C.

Sensitivity of TRMI-IMS

Under the optimum experimental conditions, we investigated the LODs of TRMI-IMS for propofol ($S/N = 3$) at different sampling times of 0.5, 1, 2, and 3 min, and they were evaluated to be 17, 8, 3, and 2 pptv respectively, which are much lower than the clinical propofol concentrations. To estimate the sensitivity enhancement of TRMI-IMS, we detected a 5 ppbv propofol sample gas by TRMI-IMS as well as CTMI-IMS, and in this experiment, the sampling time for TRMI-IMS was 1 min. As illustrated in Fig. 3, comparing to CTMI-IMS, the propofol intensity of TRMI-IMS are enhanced by a factor of 9.

Linear response range and repeatability

With a sampling time of 1 min, the calibration data points of TRMI-IMS for propofol were acquired by three individual experiments running in different days, as shown in Fig. 4. The data in Fig. 4 suggests that a satisfactory linear response for propofol can be obtained in the range of 0.1 to 2.5 ppbv. Furthermore, it should be noted that the response of TRMI-IMS

to propofol is depended on the sampling time, therefore, by adjusting this sampling time, various calibration curves for propofol can be obtained and they will provide TRMI-IMS with an overall linear response range available for the clinical setting. Additionally, the inter-day precision of the propofol intensity was calculated for each concentration, demonstrating an excellent repeatability with the average relative standard deviation (RSD) of 3.6%.

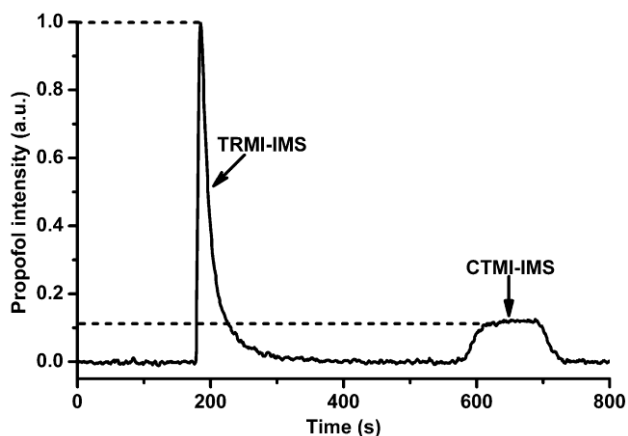


Fig. 3 Comparison of the response to 5 ppbv propofol by TRMI-IMS and CTMI-IMS.

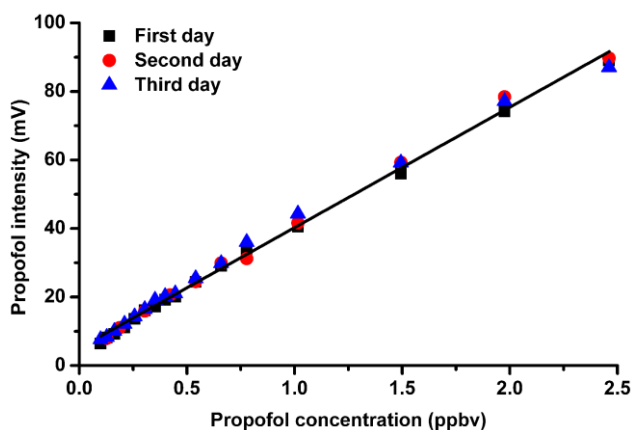


Fig. 4 The calibration curve of TRMI-IMS for propofol by three individual experiments running in different days.

15 Application of TRMI-IMS in surgery

This study protocol was approved by the Ethics Committee at Harbin Medical University (protocol no. 201314), and written informed consent was obtained from the patients prior to study enrollment. The application of TRMI-IMS in surgery was conducted at the First Affiliated Hospital of Harbin Medical University, Harbin, China. Eleven patients scheduled to undergo thyroidectomy surgery were involved in this study, and their detail data are shown in Table 1.

To induce anaesthesia, 6 $\mu\text{g/mL}$ propofol and 5 ng/mL remifentanyl were intravenously infused via a target controlled infusion (TCI) pump. To facilitate tracheal intubation, 0.2 mg/kg cisatracurium was administered. After tracheal intubation, the lungs were ventilated with an anaesthesia respirator (Dräger Fabius GS, Lübeck, Germany). Anaesthesia was maintained by continuous administration of 2.8 to 4.1 $\mu\text{g/mL}$ propofol using TCI

system, adjusted to clinical requirements. A sampling tube (Teflon) was attached to the endotracheal tube,⁷ and the breath gas was sampled continuously from this ventilator circuit. Then, the exhaled propofol concentration was measured by TRMI-IMS. As the exhaled propofol concentrations for these eleven patients were relatively high, in order to facilitate the operation of TRMI-IMS, a temperature of 90 $^{\circ}\text{C}$ was selected for both of trap and release temperature.

Fig. 5 shows the ion mobility spectra of a patient's exhaled air before and after propofol induction, from which we can see that the identification of exhaled propofol by TRMI-IMS is not affected by the clinical volatile compounds as well as the components in breath gas.

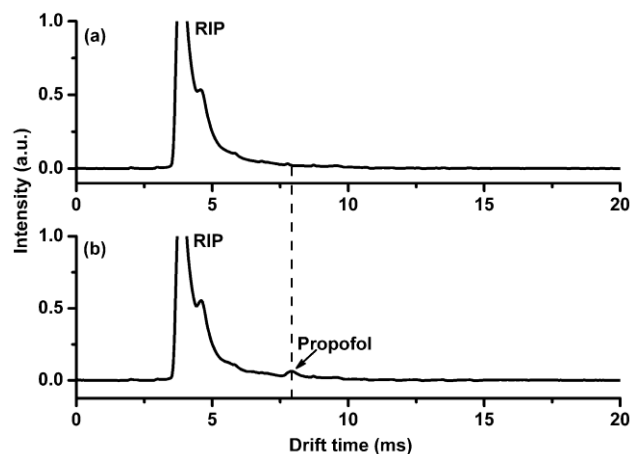


Fig. 5 Ion mobility spectra of a patient's exhaled air (a) before and (b) after propofol induction.

Taking one of these eleven patients as a typical example, at the same time as exhaled air sampling, the arterial blood was collected. The propofol concentrations in plasma were measured by high performance liquid chromatography (HPLC), and the experimental details are described in supplementary information. Fig. 6 shows the temporal profiles of exhaled propofol signal intensities obtained by TRMI-IMS, propofol concentrations in plasma measured by HPLC and calculated by TCI system, from which we can see that these profiles approximately agree with each other.

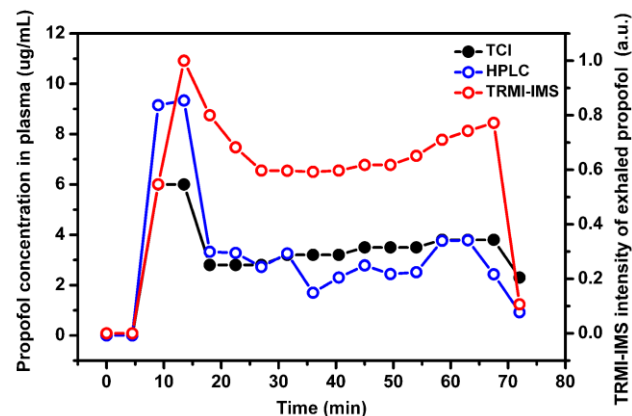


Fig. 6 Temporal profiles of the exhaled propofol signal intensity obtained by TRMI-IMS (red hollow dots), propofol concentration in plasma measured by HPLC (blue hollow dots) and calculated by TCI system (solid black dots) for a typical patient during surgery.

Furthermore, we correlated the exhaled propofol peak intensities with the calculated propofol plasma concentrations set in TCI system for the patients. As presented in Table 1, the

correlation coefficients R^2 were in the range of 0.69 to 0.93, suggesting the capability of TRMI-IMS for on-line predicting the propofol concentration in plasma.

Table 1 The detail data and correlation coefficients R^2 between the exhaled propofol TRMI-IMS signal intensities and calculated propofol plasma concentrations set in TCI system for eleven patients

Patient number	Gender	Age (yr)	Height (cm)	Weight (kg)	Correlation coefficient R^2
1	Female	58	160	70	0.85
2	Female	41	156	60	0.69
3	Female	40	158	65	0.87
4	Female	49	153	75	0.92
5	Female	51	153	47	0.87
6	Male	54	182	91	0.79
7	Female	46	160	60	0.78
8	Female	51	160	65	0.78
9	Male	49	169	61	0.93
10	Male	58	158	76	0.90
11	Male	50	162	59	0.91

Conclusion

The capability of TRMI-IMS for sensitive measurement of trace exhaled propofol has been demonstrated. Comparing to the CTMI-IMS reported previously, the sensitivity of TRMI-IMS for propofol measurement was prominently improved, and the LOD down to pptv level has been achieved, which was sufficiently sensitive to measure the exhaled propofol in clinical setting.

Furthermore, the clinical tests of TRMI-IMS were performed on eleven patients undergoing thyroidectomy surgery. The results demonstrated the potentials of TRMI-IMS for on-line predicting the propofol concentration in plasma by exhaled air measurement. Though the exhaled propofol could be readily identified using TRMI-IMS, its response factor may be affected by the matrix of breath, thus, the exact determination of the propofol concentration in exhaled air of patients should combine the standard addition method with the calibration curve, which needs further modification for our apparatus with an on-line addition unit to supply the known concentration of propofol gas.

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Notes and References

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Graphical Abstract

TRMI-IMS was constructed to improve the detection sensitivity of propofol and has been successfully tested on eleven patients undergoing surgery.

