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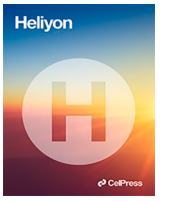

Review article

Online monitoring of propofol concentrations in exhaled breath

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ABSTRACT

Propofol, a widely used intravenous anesthetic agent, requires accurate monitoring to ensure therapeutic efficacy and prevent oversedation. Recent developments in modern analytical instrumentation have led to significant breakthroughs in on-line analysis of exhaled breath. This review discusses several sophisticated analytical methods that have been explored for noninvasive, real-time monitoring of propofol concentrations, including proton transfer reaction mass spectrometry, selected ion flow tube mass spectrometry, ion mobility spectrometry, and gas chromatography coupled to surface acoustic wave sensors. These techniques have demonstrated good correlations between plasma and exhaled propofol concentrations and between exhaled propofol concentrations and its cerebral effects. Despite these advances, the use of these technologies in clinical settings is hampered by challenges such as equipment noise, bulkiness, and high cost, as well as limitations related to endotracheal intubation, strong adsorption of propofol to components of the respiratory circuit, variability in respiratory patterns, susceptibility to changes in pulmonary ventilation and blood flow, inconsistencies in calibration methods, and the influence of other drugs and temperature fluctuations on measurement accuracy. Overcoming these technical and procedural challenges is critical to advancing the clinical application of breath analysis for propofol monitoring. This article reviews published studies and summarizes the progress and ongoing challenges in the field.

1. Introduction

Propofol (2,6-diisopropylphenol, $C_{12}H_{18}O$), synthesized by the Friedel-Crafts alkylation of phenol and propylene, was first discovered in 1970 by John Baird Glen while studying phenolic derivatives with hypnotic effects. It was not used in clinical practice until 1983, when it was introduced with a lipid emulsion as a solvent [1,2]. As a short-acting intravenous anesthetic, propofol is widely used for induction and maintenance of anesthesia due to its rapid onset and short duration of action [1,3]. Its potential antioxidant, anti-inflammatory and immunoregulatory effects have also been demonstrated [3]. However, adverse effects associated with propofol overdose are common and include hypotension, bradycardia, respiratory depression, and hypoxemia [1]. Therefore, monitoring propofol levels is of great clinical importance.

Advances in exhaled breath analysis have demonstrated significant potential for noninvasive monitoring of anesthetic agents [4,5]. Early studies using mass spectrometry techniques such as proton transfer reaction mass spectrometry (PTR-MS), selected ion flow tube mass spectrometry (SIFT-MS), and ion molecule reaction mass spectrometry (IMR-MS) have proven effective in detecting propofol in

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exhaled breath. These methods offer high sensitivity and specificity, which are critical for detecting low concentrations of propofol and ensuring accurate monitoring. Despite their potential, these mass spectrometry-based techniques have not yet become routine in clinical practice. Key barriers include the impracticality of the instruments, which are often bulky and noisy, making them unsuitable for use in the operating room. In addition, these devices require complex calibration procedures and volatile organic compounds in exhaled breath can be affected by interference from changes in pulmonary ventilation and blood flow, making them difficult to use in real-word clinical settings. Recognizing these challenges, our research aims to contribute to the body of knowledge that may eventually lead to more practical and effective solutions for real-time monitoring of propofol. Therefore, we searched PubMed, Web of Science and Google Scholar for articles using "exhaled propofol" and "expired propofol" as keywords. The VOSviewer software was used to perform a co-citation analysis of published studies, resulting in a keyword co-citation network consisting of five clusters, with a minimum citation count of three for each cluster. As shown in Fig. 1, each node represents a keyword, with its size indicating the number of published studies. The lines between the nodes indicate the strength of the co-citations, with thicker lines representing higher strengths. We found that the current research hotspots on this topic focus on "propofol concentration", "mass spectrometry", "depth of anesthesia", "PTR", "adhesion", "ppbv", "interference", "relationship", "potential", and "application". This article reviews published studies and summarizes the advances and challenges in monitoring propofol in exhaled breath.

2. Importance of propofol monitoring

In the absence of effective drug monitoring methods, anesthesiologists often use a reactive approach based on dose-response relationships to monitor anesthetic effects and make adjustments accordingly [6]. This approach is based on population models [7] and ignores inter-individual variability. Although bispectral index (BIS) values, which reflect the anesthetic effect of propofol, are often used to estimate drug concentrations, several factors can affect BIS readings, leading to unreliable results. These factors include the use of an external pacemaker [8], changes in body position [9,10], and combination with other drugs, such as ketamine [11].

Although generally considered safe, sedation practice is still associated with some morbidity and mortality [12]. In addition, accurate titration requires a high level of clinical expertise and is a labor-intensive process, potentially diverting attention from essential measures, which could paradoxically lead to suboptimal therapy or even compromise patient safety [13]. Therefore, the development of a simple concentration measurement method to guide propofol administration is essential in clinical anesthesia.

3. Monitoring through exhaled air

Exhaled breath has been explored for pharmaceutical analysis in recent years. Compared to the complex compounds found in blood, those in exhaled air are relatively simple. Nevertheless, several thousand volatile organic compounds (VOCs) have been detected in breath [14,15]. Exhaled air is warm (37 °C) and water-saturated, and its composition can be significantly affected by the breathing pattern. Therefore, patients in propofol monitoring studies are often artificially ventilated to allow continuous air sampling while avoiding confounding from inconsistent breathing patterns.

There is no consensus on how propofol is transferred from the pulmonary bloodstream to the expired air [16]. As a lipophilic drug with a low molecular weight (178.27 Da, Da), propofol diffuses more readily through alveolar capillary walls to the epithelial lining fluid [17]. One of the prerequisites for determining the concentration of propofol in expired air is its volatility [18], which is related its boiling point and saturated vapor pressure (SVP). Typically, a low boiling point and high SVP result in high volatility [19]. However, propofol is considered to have low volatility, characterized by a high boiling point (265 °C at 1 atm) and a low SVP (0.142 mmHg at 20 °C) [20]. Because of low volatility, when the bloodstream carrying propofol reaches the lungs, the headspace formed by the volatilization of free propofol passes through the respiratory membrane by passive diffusion, and the gaseous propofol is distributed from the blood into the alveoli. The SVP of propofol is much lower than that of inhalation anesthetics (e.g., sevoflurane, 156.9 mmHg

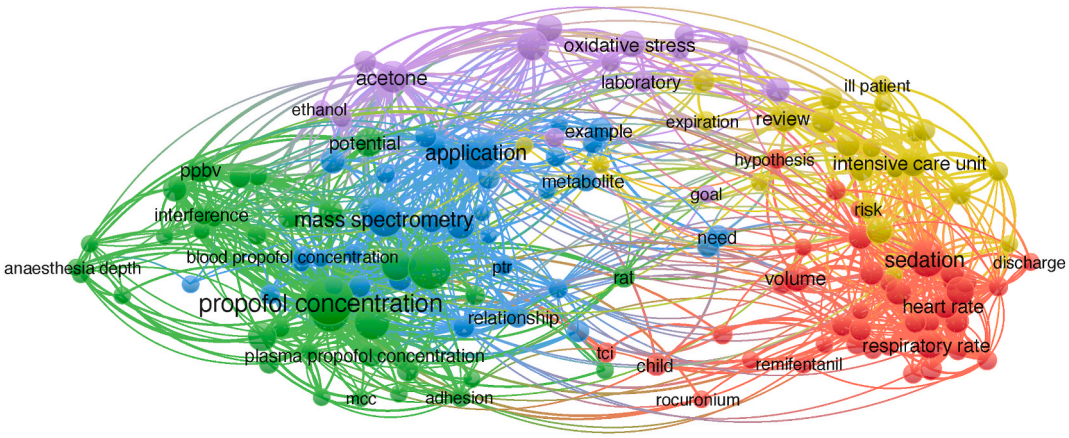

Fig. 1. The co-citation network of published studies about exhaled propofol.

at 20 °C), but higher than that of other intravenous anesthetics (e.g., fentanyl, 4.6*10^−6 mmHg at 20 °C) [21]. The blood-gas partition coefficient of propofol is substantial, ranging from 7000 to 646,000 in goats and 17,000 to 267,000 in pigs, underscoring the low volatility of propofol [22]. The relevant physicochemical properties of propofol and commonly used inhalational anesthetics are listed in Table 1 [23].

4. From offline to online monitoring

As shown in Table 2, there are currently two breath analysis methods for monitoring exhaled propofol: offline and online. The traditional and commonly used offline technique is gas chromatography-mass spectrometry (GC-MS) [24]. Since the 1970s, GC-MS has been used for breath analysis to diagnose diseases such as lung cancer, asthma, type I diabetes, tuberculosis, and organ transplant rejection [24]. Miekisch used headspace solid-phase microextraction coupled with GC-MS (HS-SPME-GC-MS) to determine the breath and plasma concentrations of propofol in 16 mechanically ventilated patients [25]. Grossherr et al. measured exhaled alveolar gas collected with Tenax tubes from 12 patients undergoing cardiac surgery by GC-MS and found that end-tidal propofol concentrations ranged from 2.8 ppbv to 22.5 ppbv [26]. Although GC-MS is considered the "gold standard" for the analysis of VOCs in exhaled breath, it is time-consuming and can only be detected off-line, which does not meet the requirements for real-time monitoring in the operating room.

Over the past two decades, the development of modern analytical instrumentation has led to significant breakthroughs in on-line analysis of exhaled breath (OLAEB) techniques for monitoring propofol concentrations [27]. One of the most important OLAEB techniques is based on mass spectrometry, in which VOCs in air samples are rapidly ionized with an ionization source and analyzed by a mass analyzer according to their mass-to-charge ratio. With continued improvements in the sensitivity and scan speed of mass spectrometers, the analysis of trace VOCs can now be completed in minutes. The mass spectrometers used include PTR-MS, SIFT-MS, and IMR-MS. In addition, other techniques such as ion mobility spectrometry (IMS) and gas chromatography coupled to the surface acoustic wave sensor (GC-SAW) have also been explored.

Targets for exhaled propofol monitoring include propofol metabolites or prototype propofol, both of which are excreted through the lungs and are well documented. Propofol is rapidly metabolized in the liver, primarily to 2,6-diisopropyl-1,4-quinoline, and excreted from the body as sulfate or glucuronic acid complexes [28,29]. Audibert's study showed that propofol metabolites can be detected in rabbit lung homogenates [30]. Similarly, Dawidowicz reported comparable ratios of propofol (central venous system/-radial artery: 1.77 ± 0.37) and 2, 6-diisopropyl, 4-quinoline (radial artery/central venous system 1.81 ± 0.59) in humans, suggesting that the human lung may play a role in the clearance of propofol by converting it to 2, 6-diisopropyl, 4-quinoline [31]. In addition, Harrison conducted a feasibility study using a PTR-MS instrument to monitor the levels of propofol and its quinone metabolites in exhaled air [32]. However, the signal generated by these metabolites is much weaker than that generated by propofol. To date, the observation peak commonly used for online monitoring of propofol is still approximately 178 Da, corresponding to the prototype drug. This represents the headspace created by the volatilization of free propofol in the bloodstream as it passes through the lungs. The concentration of propofol in exhaled breath typically ranges from 0 to 50 ppbv in humans.

5. Analytical methods for exhaled propofol monitoring

From the mass spectrometers first studied in 2003 to the IMS that has recently received much attention, various analytical instruments have produced relatively good data in monitoring propofol concentrations.

5.1. PTR-MS

PTR-MS, the earliest technique used to monitor exhaled propofol, was first developed by Werner Lindinger in the 1990s. This analytical chemistry method uses gas-phase hydronium ions (H_3O^+) as the ion source. The PTR-MS instrument is equipped with two independent compartments: one for ion generation and the other for sample ionization. At one end, the ion source is connected to a water tank. When water vapor is introduced, it is ionized to produce H_3O^+, which then enters the drift tube for sample ionization. The proton transfer process, using H_3O^+ as the ion source, can be described as follows: $H_3O^+ + M \rightarrow H_2O + MH^+$. "M" represents the measured trace VOCs that are converted to MH^+ by the proton transfer reaction with H_3O^+. Thus, VOCs in the prepared samples can be protonated for subsequent mass spectrometric detection. PTR-MS can measure exhaled air samples online with a limit of detection (LOD) at the parts per trillion by volume (pptv) level [33]. The first study to investigate the feasibility of PTR-MS in the monitoring of propofol in exhaled breath was conducted by Harrison in 2003. In this study, an unheated 4-m tube was connected to the breathing circuit of anesthetized patients undergoing gynecologic surgery, and integrated with the PTR-MS instrument. This study was the first to

Table 1
Physicochemical properties of propofol and inhalation anesthetics.

	Propofol	Ether	Halothane	Enflurane	Isoflurane	Sevoflurane	Desflurane	Nitrous oxide
Molecular Weight (Da)	178.27	74.1	197.4	184.5	184.5	200	168	44.0
Boiling point (°C) (1 atm)	256	34.6	50.2	56.5	48.5	58.5	23.5	−88.0
Vapor pressure (at 20 °C) (mmHg)	0.142	442	241	175	240	156.9	670	39000

Table 2
Summary of studies on the monitoring of propofol in exhaled breath.

	Technology	Institute	Author	Journal	Subjects	Aims
Off-line	HS-SPME-GC-MS [25]	University of Rostock, Germany	Miekisch W et al.	Clin Chim Acta. 2008	16 ventilated patients	Correlation of C_E and Cp
	GC-MS [26]	University of Luebeck, Germany	Grossherr M et al.	Br J Anaesth. 2009	12 patients underwent cardiac surgery	C_E detection: 2.8 and 22.5 ppbv
On-line	PTR-MS [32]	Queen Elizabeth Hospital, UK	Harrison GR et al.	Br J Anaesth. 2003	Patients underwent gynecological surgery	C_E detection
	PTR-MS [60]	National Defense Medical College, Japan	Takita A et al.	Anesthesiology. 2007	11 patients	Correlation of C_E and Cp
	PTR-MS [22]	University of Luebeck, Germany	Grossherr M et al.	Xenobiotica. 2009	10 pigs and 10 goats	BGPC
	PTR-MS [78]	University of Rostock, Germany	Kamysek S et al.	Anal Bioanal Chem. 2011	7 pigs	Effects of cardiac output on C_E
	SIFT-MS [34]	University of Keele, UK	Smith D et al.	Mass Spectrom Rev. 2005	5 patients underwent laparoscopic surgery	C_E detection
	IMR-MS [20]	Klinikum der Universität, Ludwig-Maximilians-University, Germany	Hornuss C et al.	Anesthesiology. 2007	Patients undergoing neurosurgery	Correlation of C_E and Cp
	IMR-MS [63]	University of Luebeck, Germany	Grossherr M et al.	Anal Bioanal Chem. 2011	Pigs	Cause of delay
	IMR-MS [26]	Klinikum der Universität München, Germany	Hornuss C et al.	Br J Anaesth. 2009	21 patients underwent surgery	C_E for anesthesia titration
	IMR-MS [72]	Klinikum der Universität München, Germany	Hornuss C et al.	J Clin Monit Comput. 2013	40 patients	Expiratory Isoprene for expiratory phase monitoring
	IMS [40]	University of Göttingen, Germany	Perl T et al.	Br J Anaesth. 2009	13 patients underwent otorhinolaryngologic surgery	Correlation of C_E and Cp
	IMS [41]	Technische Universität Berlin, Germany	Kreuder, AE et al.	Int J Ion Mobil Spec. 2011	Patients	Correlation of C_E and Cp
	IMS [46]	Dalian Institute of Chemical Physics, China	Zhou QH et al.	Talanta. 2012	Mice	Interference of moisture
	IMS [47]	Dalian Institute of Chemical Physics. China	Zhou QH et al.	J Breath Res. 2015	Patients undergoing mastectomy	Interference of moisture
	IMS [48]	Dalian Institute of Chemical Physics, China	Jiang D et al.	Anal Chim Acta. 2021	7 patients	Interference of moisture
	IMS [49]	Dalian Institute of Chemical Physics, China	Jiang D et al.	Anal Chem. 2018	1 patient undergoing laparoscopic distal pancreatectomy combined with cholecystectomy	Interference of sevoflurane
	IMS [50]	Dalian Institute of Chemical Physics, China	Jiang D et al.	Talanta. 2020	Patients underwent gastric cancer surgery	Interference of sevoflurane
	IMS [62]	University of Oslo, Norway	Braathen MR et al.	Acta Anaesthesiol Scand. 2022	29 patients underwent laparoscopic cholecystectomy or bariatric surgery	Moderate correlation of C_E and Cp
	IMS [68]	Dalian Institute of Chemical Physics, China	Liu Y et al.	Acta Anaesthesiol Scand. 2015	19 patients underwent surgery	C_E for anesthesia titration
	IMS [69]	Hannover Medical School, Germany	Heiderich S et al.	BMC Anesthesiol. 2021	Pediatric patients	C_E for anesthesia titration
	IMS [61]	Saarland University Medical Center, Germany	Müller-Wirtz LM et al.	Anesth Analg. 2021	Rats	Correlation of C_E and propofol concentration in brain tissues of rats
	IMS [74]	Saarland University Medical Center, Germany	Maurer F et al.	J Pharm Biomed Anal. 2017	/	Analytical method validation
	IMS [75]	Saarland University Medical Center, Germany	Maurer F et al.	J Pharm Biomed Anal. 2017	/	Analytical method validation
	IMS [81]	Dalian Institute of Chemical Physics, China	Zhou QH et al.	Anal Methods. 2014	/	Preparation of standard gas

(*continued on next page*)

Table 2 (*continued*)

	Technology	Institute	Author	Journal	Subjects	Aims
	IMS [74]	Saarland University Medical Center, Germany	Maurer F et al.	J Breath Res. 2017	/	Adsorbability of propofol
	IMS [73]	Saarland University Medical Center, Germany	Lorenz D et al.	J Breath Res. 2017	/	Adsorbability of propofol
	IMS [82]	Saarland University Medical Center, Germany	Maurer F et al.	Int J Anal Chem. 2019	/	Transportation and storage of propofol gas samples
	IMS [70]	Saarland University Medical Center, Germany	Hüppe T et al.	Acta Anaesthesiol Scand. 2023	30 patients scheduled for lung surgery	Quantification of C_E during single-lung ventilation
	GC-SAW [52]	Zhejiang University, China	Chen X et al.	Br J Anaesth. 2014	28 patients	Correlation of C_E and Cp
	GC-SAW [53]	Zhejiang University, China	Zhang F et al.	Anal Sci. 2017	6 patients	Correlation of C_E and Cp
	GC-SAW [54]	Zhejiang University, China	Dong H et al.	J Chromatogr A. 2017	Patients	Correlation of C_E and Cp
	GC-SAW [77]	Zhejiang University, China	Dong H et al.	Anesth Analg. 2020	Patients	Modified BGPC
	PAS [56]	University of Cambridge, UK	Laurila T et al.	Anal Chem. 2011	/	Exploration of new technologies
	DMS [57]	Dalian Institute of Chemical Physics, China	Li Y et al.	Anal Methods. 2021	1 patient underwent thyroidectomy	Exploration of new technologies
	LTP-MS [58]	Texas Tech University, USA	Gong X et al.	J Am Soc Mass Spectrom. 2022	/	Exploration of new technologies

Note: HS-SPME-GC-MS, the headspace solid-phase microextraction technique coupled with gas chromatography-mass spectrometer; GC-MS, gas chromatography-mass spectrometer; C_E, concentration in exhaled breath; C_p, concentration in plasma; PTR-MS, proton transfer reaction mass spectrometry; BGPC, blood gas partition coefficient; SIFT-MS, selected ion flow tube mass spectrometry; IMR-MS, ion molecular reaction mass spectrometry; IMS, ion mobility spectrometry; GC-SAW, gas chromatography combined with surface acoustic wave sensor; PAS, Photoacoustic spectroscopy; DMS, differential mobility spectrometry; LTP-MS, low-temperature plasma desorption ionization mass spectrometry.

demonstrate that PTR-MS can detect exhaled propofol in real time [32].

PTR-MS has excellent sensitivity and provides rapid results, which are critical for real-time monitoring applications. Its method of soft ionization minimizes fragmentation of the analyte, thus preserving the molecular integrity of propofol. However, PTR-MS instruments are typically bulky and produce significant noise, which can be disruptive to the clinical environment. Their inability to discriminate between compounds with similar mass-to-charge ratios without additional MS/MS capabilities is a limitation for complex mixture analysis.

5.2. SIFT-MS

SIFT-MS was developed at the University of Birmingham in the mid-1970s. It uses either positive ions (H_3O^+, NO^+ and O_2^+) or negative ion chemical ionization (O^-, OH^-, O_2^-, NO_2^- and NO_3^-) as precursor ions to react with VOCs in exhaled breath. These ion fragments are then filtered through a quadrupole mass filter for mass analysis. SIFT-MS also has high sensitivity with an LOD in the pptv range [34]. Boshier first used the SIFT-MS instrument to analyze the expired concentrations of propofol, isoprene and acetone in five anesthetized patients undergoing laparoscopic surgery, where the SIFT-MS instrument was connected to the endotracheal tube via a 5-m-long PEEK capillary tube. This study was the first to demonstrate the potential of SIFT-MS for monitoring endogenous respiratory metabolites, anesthetic gases, and biomarkers of metabolic and oxidative stress in the perioperative period [35].

SIFT-MS allows the simultaneous analysis of multiple compounds and does not require prior separation, making it highly efficient for rapid screening. However, similar to PTR-MS, the instrumentation is large and can be noisy. Calibration can be complex because it must account for potential reactions between the precursor ions and various background gases.

5.3. IMR-MS

The IMR-MS system is based on ion-molecule reactions coupled to quadrupole mass spectrometry. After gas samples are introduced to the IMR-MS instrument, the propofol molecules react with the positively charged mercury ions to form product ions. These ions are then separated by a quadrupole mass separator and quantified by a secondary electron multiplier. Upon ionization, propofol molecules produce two product ions, with mass-to-charge ratios of 163 and 178, respectively. IMR-MS is characterized by high sensitivity, rapid response, and LOD down to the ppbv level [36]. Hornuss and colleagues used an IMR-MS instrument to automatically measure the propofol headspace produced by the blood of neurosurgical patients. They also used another IMR-MS system to measure end-tidal propofol concentration online and found that propofol headspace is closely related to whole blood propofol concentration [20].

IMR-MS provides highly sensitive detection and can be tailored to detect specific molecules through the selective reaction processes. However, the technology is susceptible to changes in environmental conditions such as temperature and humidity, which can significantly affect its accuracy and reliability.

5.4. IMS

IMS separates and identifies different VOCs from samples based on the time it take the ions to pass through the drift tube, and it does not require sample pre-teatment. IMS has been used to identify VOC biomarkers in exhaled breath samples for diseases such as lung cancer [37], Alzheimer's disease [38], and Parkinson's disease [39]. Coupled with the multi-capillary column (MCC), IMS has been extensively studied for the direct quantification of propofol in exhaled breath. In 2009, Perl first used MCC-IMS to measure exhaled propofol concentration in 13 patients undergoing elective ENT surgery, and compared these measurements with the plasma propofol concentrations measured by GC-MS, demonstrating that MCC-IMS may be a suitable method for determining exhaled propofol concentrations and a potential tool for predicting plasma propofol concentrations [40]. In 2011, Kreuder and colleagues confirmed the reliability of MCC-IMS in measuring exhaled propofol concentrations [41]. Due to its relatively low cost, portability, suitable measurement range, and certain humidity resistance through the multi-capillary columns, MCC-IMS is considered the most promising technology suitable for development and translation into products. The Edmon® bedside online propofol monitor from Germany is an instrument based on MCC-IMS technology.

Although IMS instruments are small and inexpensive, making them potentially suitable for clinical settings [42], high humidity in exhaled breath can affect the ion drift time, thus degrading IMS detection performance. This includes a reduction in selectivity and sensitivity [43]. In fact, the humidity of breath samples can vary significantly during mechanical ventilation, further complicating to the use of these devices [44]. Although MCC technology, which pre-separates gas samples to mitigate the influence of the high humidity of human breath, is used in the Edmon® devices, studies have shown that residual humidity can still significantly degrade measurement performance [45]. Several researchers have developed various methods to eliminate humidity interference, including MI-IMS, time-resolved dynamic dilution introduction, and real-time humidity correction in unidirectional anisole-assisted photoionization ion mobility spectrometry [46–48]. However, these methods have had limited success. In addition to humidity, sevoflurane can also affect the accuracy of monitoring. During the IMS ionization process, the ion fragment of sevoflurane with a mass charge ratio of 163 overlapped with that of propofol. Jiang et al. sequentially developed acetone-assisted negative photoionization IMS and anisole-assisted photoionization IMS to eliminate the interference of sevoflurane in exhaled breath [49,50]. However, these technologies are still in the research and development stage and have not been commercialized.

5.5. GC-SAW

The surface acoustic wave (SAW) sensor is a type of sensor based on a high-frequency mechanical oscillator, that provides a simple and sensitive method for detecting gas-phase substances. The elastic substrate surface of the SAW sensor can be coated with various selective materials. The adsorption and desorption of VOCs in breath on this coating can change its mass and the conductivity of the chemical interface, thus affecting the amplitude and phase velocity of the SAW sensor. The sensor is highly sensitive, with an LOD that can reach the pptv level. In addition, the selectivity of the SAW sensor can be controlled by functionalizing the resonator with different coating materials [51]. In 2014, Chen and colleagues used a GC-SAW system to test 28 patients receiving intravenous propofol and demonstrated its reliability and efficiency in the simultaneous quantitative determination of propofol concentration in blood and exhaled breath [52]. In 2017, Zhang et al. introduced a virtual surface acoustic wave sensor array (VSAWSA) to noninvasively detect the propofol concentration in blood via expired breath in 6 patients. Clinical monitoring data from the VSAWSA showed excellent agreement with target values [53]. In addition, Dong et al. used GC-SAW to simultaneously monitor exhaled concentrations of sevoflurane and propofol online, and found that all monitored concentrations were in excellent agreement with drug consumption, demonstrating the efficacy of rapid GC-SAW for propofol monitoring [54]. However, the instrument has a minimum measurement interval of 90 s, which may miss some critical concentration information.

This combination allows for high specificity and the ability to analyze complex mixtures due to the effective separation by GC and sensitive detection by SAW. However, the main disadvantage is the slower analysis time due to the need for chromatographic separation.

5.6. Other breath analysis techniques

In addition to the methods described above, several other techniques are under investigation for the monitoring of exhaled propofol. Photoacoustic spectroscopy (PAS) is a background-noise free signaling technique in which a modulated laser generates sound waves in a gas sampling cell. These waves are detected by a microphone and converted to an electrical signal. A commonly used optical detection method is the measurement of exhaled nitric oxide for the clinical diagnosis of asthma [55]. Laurila et al. quantitatively measured the absorbance of exhaled propofol in both the ultraviolet and mid-infrared spectral regions, marking the first use of optical spectroscopy to detect propofol from patients' exhaled breath. The study achieved an LOD in the subparts per billion concentration range [56]. Li et al. developed a differential mobility spectrometry (DMS) device characterized by smaller size, faster response time and lower cost. This device demonstrated the capability of sensitive and continuous breath-by-breath measurement of trace amounts of exhaled propofol in a patient undergoing thyroidectomy [57]. Gong et al. developed a low-temperature plasma desorption ionization mass spectrometry instrument, which has the additional advantages of cost-effectiveness and better sample storage [58,59]. However, these technologies have only been reported in one or two scientific studies, and it remains uncertain whether they can be effectively translated into commercial products.

As mentioned above, the instruments currently used for such studies include both mass spectrometers and non-mass spectrometers. Each of these technologies offers unique advantages for monitoring propofol in exhaled breath, such as high sensitivity and the ability to provide real-time data. However, mass spectrometers often present challenges such as noise, bulkiness, and high cost, making it difficult to adapt them for use in the operating room. Addressing these issues, particularly through the development of more compact, quiet, and robust instruments, is essential for their future integration into clinical settings.

6. Application of exhaled propofol monitoring

6.1. Correlation of propofol concentrations in the breath and plasma

One of the primary goals of exhaled propofol monitoring is to predict plasma concentrations, a strong correlation that has been demonstrated in many studies using different devices. Takita et al. continuously measured exhaled propofol concentrations in 11 intubated patients who were infused with propofol at rates of 3, 6, or 9 mg/kg/h for 60 min using PTR-MS, and compared these measurements with blood samples. The results showed that volatile propofol was detectable in all patients, and there was a good correlation between plasma and exhaled propofol concentrations [60]. Similarly, Chen's study using the fast GC-SAW instrument reported a correlation coefficient of 0.982, while Müller-Wirtz's study using the MCC- IMS instrument reported a correlation of 0.71 [52,61]. However, not all studies support these results. Braathen et al. used the Edmon® to predict plasma propofol concentration in normal weight and obese patients and found only a moderate correlation ($R^2 = 0.58$), which casts doubt on the clinical utility of this technique [62].

In addition, studies have shown a significant delay in exhalation as blood propofol concentrations change [20]. To investigate the reasons for this delay, Grossherr et al. administered ethanol and propofol alone or in combination, to 8 endotracheally intubated pigs and monitored the signals by IMR-MS. The response showed that ethanol appeared and reached its peak concentration significantly earlier than propofol, suggesting that the delay in exhaled propofol may be due to its pharmacological and physicochemical properties [63].

6.2. Correlation between the exhaled propofol concentration and its cerebral effects

Another important goal of exhaled propofol monitoring is to predict the cerebral effects of propofol. The concentration of propofol

in the blood peaks immediately after intravenous injection, while the increase in the brain and the onset of unconsciousness are delayed [64]. This hysteresis is caused by the time it takes for the plasma concentration to equilibrium with the concentration at the site of action in the central nervous system [65,66]. Interestingly, a similar delay is observed in exhaled propofol concentrations. Hornuss used IMR-MS to measure the time course of exhaled propofol concentrations in 21 patients and monitored BIS to measure the cerebral effects of propofol. They found that, after an IV bolus dose, the time to detection and peak concentration of exhaled propofol were similar to those observed in BIS, suggesting that exhaled propofol concentrations may be useful for titrating intravenous anesthesia [67]. Similarly, Liu et al. reported that exhaled propofol concentration measured by membrane inlet-ion mobility spectrometry (MI-IMS), was correlated with BIS and concluded that monitoring exhaled propofol could improve the safety of anesthesia [68].

Studies have shown that the correlation between propofol gas concentration and anesthetic effect is evident not only in adults but also in children. Heiderich and colleagues used the MCC-IMS to demonstrate good correlations between the exhaled propofol concentration and the Narcotrend Index in pediatric patients during both induction and maintenance of anesthesia. However, these correlations are highly variable [69]. This variability is largely due to the fact that EEG variability is relatively high, and the same depth of anesthesia may correspond to different values, which is also a major limitation of EEG monitoring. In an effort to address this issue, Müller-Wirtz used MCC- IMS to directly compare the concentration of propofol in exhaled breath with that in brain tissue and found a good correlation between the two [61], supporting the idea from a pharmacokinetic perspective that monitoring the concentration of propofol in exhaled breath may help to estimate cerebral anesthetic effects.

7. Challenges in exhaled propofol monitoring

Although several analysis techniques have been employed that have led to significant advances in exhaled propofol monitoring have been employed, several significant and persistent challenges remain that impede further development. These include limitations due to endotracheal intubation, strong adsorption of propofol to plastic tubing, susceptibility to variations in pulmonary ventilation and pulmonary blood flow, and inconsistent calibration methods. Therfore, future studies should urgently address these issues to facilitate the translation of breath analysis into effective propofol concentration monitoring.

7.1. Alveolar gas collection

A stable tidal volume is essential for air sampling in concentration monitoring. In published studies, all subjects were endotracheally intubated to facilitate air sampling and comparisons of concentration at different time points. However, propofol is also widely used in gastrointestinal endoscopy, where endotracheal intubation is not performed. Varying expiratory volumes, inconsistent respiratory rates, and respiratory depression make monitoring difficult due to differences in inspired volumes. In addition, exhaled propofol monitoring is not feasible during single-lung ventilation with a double-lumen catheter. Hüppe and his colleagues observed that exhaled propofol concentrations unexpectedly increased by approximately one-third during single-lung ventilation, limiting the use of exhaled propofol monitoring in such scenarios [70]. Despite the use of endotracheal intubation, the collecting of alveolar gas-the drug containing gas produced in the alveoli-remains difficult.

There are two methods of collecting expired air samples. One is to collect mixed expired air, and the other is to collect pseudo alveolar gas based on the waveform of the end-expiratory CO_2 curve. The CO_2 in the alveolar gas forms the plateau of the CO_2 curve. By analyzing this CO_2 curve, the sample gas approximating the alveolar gas can be collected either manually by controlling the sampling port switch or continuously in real time using a manufactured alveolar gas collection device. The principle of the latter is to consider CO_2 levels $\geq$25 mmHg (or higher) as indicative of alveolar gas. This approach is necessary because CO_2 is often undetectable by many mass spectrometers. Some researchers have suggested using stable VOCs in exhaled breath as an alternative criterion. Hornuss designed studies to investigate whether isoprene could replace CO_2 for identifying the expiratory phase and found that the expiratory propofol signals obtained with both methods were similar [71,72].

7.2. Adhesion of propofol to plastic tubes

Propofol is synthesized from phenol and propylene, which are also key components to the manufacture of plastics, which may explain the ability of propofol to adhere to plastics [73]. It is important to note that the materials used in breathing circuits vary, and the adhesion of gas-phase propofol to plastic tubing in these circuits complicates quantification and may lead to measurement error. To improve measurement accuracy, the amount of adhesion should be further measured and analyzed according to the specific material used.

Maurer reported that perfluoroalkoxy (PFA) tubing has the lowest adsorptivity and shortest desaturation time, followed by polytetrafluoroethylene (PTFE) tubing. Conversely, silicone, polyurethane (PUR), and Tygon tubes are less suitable for sampling gaseous propofol, especially the latter two, which absorb all gas-phase propofol [74]. Propofol reversibly binds or adsorbs to polyvinyl chloride (PVC) loops via saturation kinetics and does not diffuse outward through plastic surfaces [73]. In addition, propofol can be absorbed by polystyrene materials [75]. Sautouo-Miranda et al. reported that polypropylene or glass containers did not significantly reduce propofol concentrations [76]. However, the concentration of liquid propofol (0.1–3 mg/mL) used in Sautouo-Miranda's study was much higher than that typically found in exhaled air, raising questions about the applicability of these results to gaseous propofol. Moreover, studies have shown that the increase in propofol concentration at the ventilator end is significantly less than that at the endotracheal tube end, suggesting that the sampling site should be close to the patient end to minimize variations caused by propofol adsorption [32,73].

7.3. Susceptibility to pulmonary ventilation and pulmonary blood flow

Theoretically, all factors affecting pulmonary blood flow, pulmonary ventilation, pulmonary exchange, and the ratio of pulmonary ventilation to blood flow can affect the concentration of propofol in exhaled breath. These complexities greatly increase the difficulty of intraoperative quantitative monitoring of end-tidal propofol concentration.

Dong and colleagues proposed a new correction method to mitigate the influence of respiratory factors on exhaled propofol monitoring by using a ventilation-based modified blood/expired gas partial pressure ratio [77]. However, this correction method lacks sufficient data for further verification, which casts doubt on its validity. It has also been reported that patient cardiac output may influence exhaled propofol concentrations [78]. Kamysek et al. reported that dobutamine-induced increases in cardiac output worsened the correlation between expired and plasma propofol concentrations in pigs, whereas reduction in cardiac output by pulmonary artery ligation did not significantly affect the correlation [78]. These conflicting results highlight the need for further verification by future studies.

7.4. Inconsistent calibration methods

Breath samples are characterized by high levels of endogenous metabolites with significant inter-individual variability. Therefore, it is crucial to establish an accurate and reliable calibration method tailored to the structure of propofol and its expected concentration range. The detection method must also be rigorously validated. Recommended validation steps include constructing a standard curve and examining the detection range, detection limit, precision, accuracy, carryover effects, and sample stability [79,80]. Among these, the preparation of the propofol standard gas sample poses a significant challenge.

The traditional method for obtaining propofol calibration gas involves the use of a commercially available dual-channel VOCs generator. In this system, one channel is used to accurately inject the propofol solution via a precision pump, while the other channel is controlled by a flow controller to purge the gas into a carburetor. Here, the propofol solution is stably vaporized at 40 °C or 100 °C and then mixed with a carrier gas to produce a continuous flow of propofol calibration gas. Previous studies have used VOC generators such as the MF-3B gas generator (China National Metrology Technology Development Co., Beijing, China) [54], and the HovaCAL 4836 gas generator (IAS GmbH, Oberursel, Germany) [74,79,80]. Solvents such as methanol, ethanol or water are often used to prepare propofol solutions [80]. However, due to the high boiling point of propofol, this method faces the challenge of incomplete volatilization.

Chinese scholars have proposed a method to prepare calibration gas using the headspace of propofol [46]. First, 0.5 mL of liquid propofol is drawn and sealed in a 2 mL brown reagent bottle. Next, the needle of a 1 mL disposable syringe is used to puncture several holes in the silicone rubber pad of the bottle cap; this assembly is then placed in a gas distribution bottle, where a constant flow of clean air is supplied to purge and mix with the gaseous propofol molecules diffusing from the reagent bottle. After a period of time, the weight loss of the reagent bottle is measured using a weighing method, and the concentration of virgin propofol gas is calculated from this data.

$$C = \frac{22.4\, m}{M f_1 t} * \frac{273 + T}{273} * 10^9$$

Where C is the concentration of the prepared propofol calibration gas (ppbv). The variable m is the mass difference (g) of the propofol reagent bottle before and after purging over the period t. M stands for the molar mass of the propofol, which is 178.27 g/mol. The flow rate of the purge gas is represented by f_1 (L/min), t is the purging time (min), and T is the internal temperature (K). By adjusting the purge gas flow rate, different concentrations of propofol standard gas samples can be obtained. This method indirectly calculates the mass of propofol in the headspace by measuring the weight loss of the reagent bottle, which avoids the problem of incomplete volatilization of liquid propofol and improves the accuracy of the standard gas samples. Diffierent concentrations of propofol calibration gas can be achieved by controlling different flow rates through the flow controller [57,81]. Additionally, the standard gas should be prepared and used immediately, and it should be refrigerated during transport or storage to minimize loss [82].

7.5. Other limitations

Few studies have examined the influence of other drugs on the monitoring of exhaled propofol concentrations. Clinically, propofol is often administered in combination with other sedatives, such as midazolam, etomidate and dexmedetomidine, analgesics such as fentanyl and sufentanil, and muscle relaxants. The synergistic or antagonistic interactions between these drugs can significantly affect the correlation between propofol concentration and sedative effect. Furthermore, research suggests that some anesthetic agents may enhance the pulmonary first-pass uptake effect, thereby altering the pulmonary gas exchange of propofol, either increasing or decreasing it [83,84]. Temperature is another important factor. Body temperature can affect the concentration of propofol in the alveolar air, while operating room temperature can affect the adsorption of propofol on plastic surfaces used in medical devices.

8. Conclusions

The development of a novel and simple method to determine propofol concentration to guide titration in clinical anesthesia is highly desirable, and exhaled air monitoring holds great promise. This review comprehensively summarizes the current progress in exhaled propofol monitoring, highlighting the use of advanced technologies such as PTR-MS, SIFT-MS, IMR-MS, IMS and GC-SAW.

With the advancements of modern analytical instrumentation, breakthroughs have been made in on-line breath analysis techniques. There are good correlations between plasma and exhaled propofol concentrations and its cerebral effects. Despite these advances, suitable devices for exhaled propofol monitoring remain elusive. Moreover, challenges such as the limitations of endotracheal intubation, strong adsorption to breathing tubes, susceptibility to variations in pulmonary ventilation and blood flow, inconsistencies in calibration methods, and interference from other drugs and temperature variations have hindered further development of online exhaled propofol monitoring.

To improve the accuracy and reliability of propofol monitoring, future research should focus on: First, innovations in sensor technology and analytical methods that can withstand the operational challenges of clinical environments. Second, robust calibration protocols that can adapt to variable surgical settings should be established. Third, combining propofol monitoring with other monitoring systems can provide a holistic view of the patient's status, potentially imporve the accuracy of predicting depth of anesthesia. Moreover, further investigation of how propofol interacts with other commonly used anesthetic agents may lead to a better understanding and management of the combined effects on monitoring outcomes. In conclusion, although significant progress has been made in the field of propofol monitoring, continued research and technological development are essential to overcome current limitations and improve the safety and efficacy of anesthesia management. Therefore, future research must address these issues to enable the true translation of online monitoring of exhaled propofol concentration into clinical practice.

CRediT authorship contribution statement

Xiaoxiao Li: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Pan Chang:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Wensheng Zhang:** Project administration, Funding acquisition, Conceptualization.

Data availability statement

We will provide raw data and materials when required after being published: scu_wc93@163.com.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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