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Progress of artificial intelligence in anesthesia and perioperative medicine

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Highlights

- This review introduces the core concepts of artificial intelligence (AI) and describes the most commonly encountered computerized functioning of AI in anesthesiology.
- This survey systematically presents the main clinical applications of AI in anesthesia and perioperative medicine according to the perioperative phases.
- The advantages and disadvantages of introducing AI into the medical field are also discussed to explore the career development direction of anesthesiologists in the future.

Abstract

Perioperative medicine is a series of medical activities throughout the perioperative period, including preoperative optimization, intraoperative safety, postoperative rehabilitation, and other activities. Anesthesia is closely integrated with perioperative medicine to guarantee smooth progress of operations, comfortable recovery, and favorable long-term outcome for patients. There are a huge number of clinical data in anesthesia and perioperative medicine, and artificial intelligence (AI) has a powerful ability to analyze and evaluate data; thus, applying AI is a significant advantage in analysis and prediction based on real clinical big data in anesthesia and perioperative medicine. AI has made some progress in the field of anesthesiology and perioperative medicine. This review introduces the most encountered computerized techniques of AI in anesthesiology, main clinical applications themes of AI in anesthesiology, as well as limitations and ethical implications involved in deployment of this technology.

Keywords: Anesthesia, artificial intelligence, machine learning, perioperative medicine

Introduction

Artificial intelligence (AI) is defined as the broad concept of machines designed to imitate the human way of thinking by building a model and finding some rules of the data on their own. The various techniques of AI include machine learning (ML), deep learning (DL), and natural language processing (**Figure 1**) [1]. In addition to the patients' health data, there are likewise substantial perioperative monitoring data as anesthesia runs through the whole perioperative period, which creates opportunities for the application of AI in the field of anesthesia.

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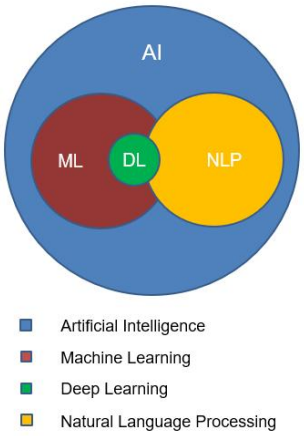

Figure 1. Artificial intelligence. AI, artificial intelligence; DL, deep learning; ML, machine learning; NLP, natural language processing.

Namely, the characteristics of anesthesiology as a data-intensive discipline make it most likely to benefit from the advances in AI [2].

Machine learning

ML is currently the most dominant approach to achieve AI, wherein a computer generates underlying rules by processing raw data and expected answers from the data. ML is an appropriate method for anesthesiology, providing the capability to analyze plentiful clinic data (e.g., Bispectral index (BIS)), discover associations, generate latent rules, and predict the outcomes through continuous learning, which is strikingly similar to the doctor's diagnostic process [3]. Predicting the incidence of postoperative complications caused by clinical factors based on big data analysis is a typical application of ML in anesthesia. According to the learning manner, it includes supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning.

- Supervised learning is a process by which an algorithm is trained with the input eigenvalue and the target value.

  Decision tree model is a basic classification and regression method that presents a tree structure and classifies instances based on input features.

  The k-nearest neighbor algorithm is another essential classification and regression approach, in which the category of each instance can be represented by the category of its k nearest neighbors (e.g., based on Euclidian distance).

- Unsupervised learning is a ML technique where a model is trained only with the input eigenvalue without the target value.

- Semi-supervised learning is a hybrid approach that combines aspects of both supervised learning and unsupervised learning where the model is trained using input eigenvalue and a subset of the target value.

- Reinforcement learning refers to the process by which an algorithm is asked to attempt a certain task, and it will be given different rewards or punishments according to the completion of the task, then the computer will automatically optimize a criterion based on this reward or punishment, which is also a learning method used by AlphaGo.

Deep learning and neural network

DL is a subset of ML that utilizes multiple layers of connected neural networks, like the human brain, to progressively extract higher-level features from the raw inputs [3]. The most representative algorithms of DL networks are convolutional neural networks (CNNs), which can better process data with a grid-like structure, such as image data that can be viewed as two-dimensional grid of pixels (**Figure 2**). Recurrent neural networks are known as "memory" network of DL, which are sensitive to the sequence of the input. Therefore, recurrent neural networks are effective in mining temporal and semantic information from sequential data such as speech [4]. The strength of DL over traditional ML is that multi-layer mapping of neural networks can automatically learn complex data features, which reduces the workload of feature engineering by a human expert [2]. For example, CNNs are applied to predict difficult airway intubation based on preoperative pictures of patients. These networks utilize a simple neuron-level approach to process signals and then parameterize the connections between neurons by weights.

This review introduces AI techniques currently applied in anesthesia research and describes the current state at the cross-disciplines of AI and anesthesia. A literature search was conducted using the keywords "artificial intelligence", "anesthesia", and "perioperative period" in the PubMed database. This review is divided into sections dealing with most encountered computerized techniques in anesthesiology, main clinical applications of AI in perioperative anesthesiology, and limitations and ethical implications involved in deployment of AI.

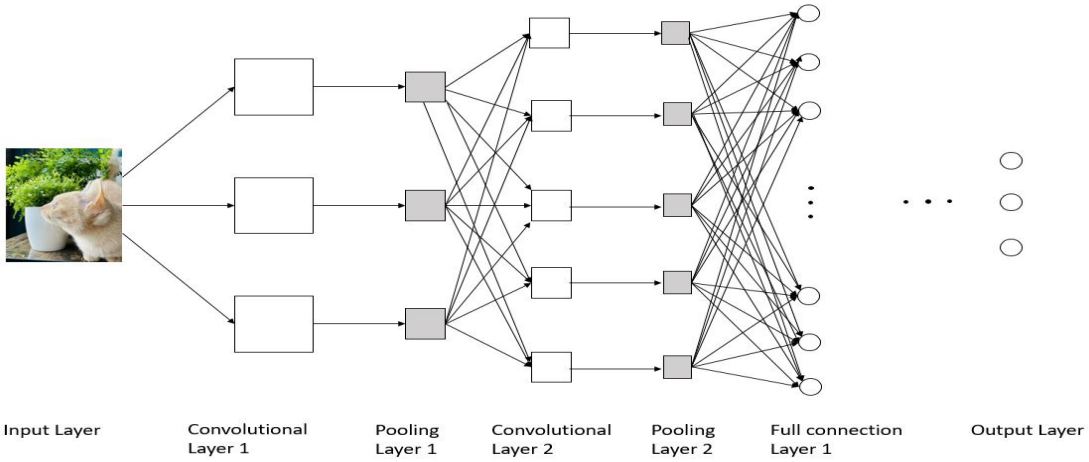

Figure 2. Architecture of convoluted neural networks. The input image is passed through the convolutional neural network model to output the classification result. The box represents the image matrix; the circle represents the neuron; the arrow represents the direction of data movement. Structures associating a convolutional layer and a pooling layer can be used consecutively. Full connection layer can also be used consecutively. The output layer is also referred to as the classification layer since output neurons classify the inputs into one of the output categories.

AI in pre-operative anesthesia

Preoperative risk prediction

Risk stratification is a primary but very important step of anesthesia, and risk prediction is the most common application field of AI in preoperative assessment. However, traditional preoperative anesthesia classifications are manually reviewed by clinicians, with certain subjectivity and limited granularity. Supervised ML methods, specifically random forest split classification, have been tested to automatically generate an American Society of Anesthesiologists Physical Status rating with finer granularity which may be able to aid anesthesiologist in identifying at-risk patient [5].

Multiple systems for preoperative risk prediction have been proposed to improve existing scores such as American Society of Anesthesiologists Physical Status, and some even defined extra patient-specific risk scores. For example, a famous system called "MySurgeryRisk" collected data from 51,457 patients undergoing different types of surgeries, and picked 285 preoperative parameters for each patient to generate a risk score by using ML [6]. Moreover, many scholars have optimized perioperative risk prediction with better algorithms and superior performance. For example, Fritz et al. developed a multipath CNN model from the data of 95,907 surgical patients, and for each patient, 56 preoperative parameters were selected to predict the risk of death within 30 days [7]. This algorithm has been shown to have better performance with higher area under the curve (AUC) value when compared to that of CNN model, random forest model, support vector machine, and logic regression algorithm.

Difficult intubation prediction

Difficult tracheal intubation is the main cause of anesthesia-related morbidity and mortality. Although video laryngoscopy has been widely used in clinical practice, difficult intubations are still frequently encountered. Preoperative airway assessment is an important part of perioperative anesthetic management. Airway examination is another highly operator-dependent assessment. Therefore, an objective method is needed to define the degree of airway difficulty. Hayasaka et al. developed a CNN algorithm capable of evaluating the difficult intubation with an AUC of 0.864 by evaluating patients' facial pictures in the supine-side-closed mouth-base position [8]. Matava et al. critically assessed the use of AI and ML in the assessment, diagnosis, monitoring, procedure assistance, and outcome prediction during pediatric airway management [9].

In addition to AI face recognition analysis techniques that can be used to predict difficult intubation, acoustic features can also predict difficult intubation. The acoustic data of 225 patients who underwent orthognathic surgery under tracheal intubation were collected during preoperative clinical airway assessment, and logistic regression analysis was performed to examine the association between acoustic features and difficult laryngoscopy. The obtained model identified the difficult intubation with an AUC of 0.724, an overall accuracy of 0.632, a

specificity of 0.582, and a sensitivity of 0.772 [10]. Acoustic features show the potential for predicting difficult intubation among patients under general anesthesia.

AI-assisted intra-operative anesthesia

Intubation and extubation operation

Intubation is one of the most important anesthetic skills. In 2012, Hemmerling et al. developed a robotic intubation system (Kepler intubation system) for oral tracheal intubation [11]. In this operating system, doctors can remotely use a joystick to control a video laryngoscope and safely insert an endotracheal tube into the patient's trachea. The success rate reached 91% at the first human testing of this system. Although it was the first time to validate and realize the possibility of remote control of tracheal intubation, the system did not strictly reflect AI. Moreover, the system could not quickly identify the trachea to achieve tracheal navigation in difficult airway. In one patient of this study, fogging of the video laryngoscope hindered the intubation using Kepler intubation system.

In the context of coronavirus disease 2019 (COVID-19) pandemic, Wang et al. developed a new tracheal intubation device based on magnetic navigation technology [12]. The new tracheal intubation device was designed by using external magnets to guide corresponding magnets in the body to move towards a preset target area. The tracheal intubation based on magnetic navigation technology is feasible, with high efficiency and easy operation. This magnetic navigation tracheal intubation enables successful tracheal intubation and takes less time than that of traditional laryngoscopy; more importantly, it reduces the risk of occupational exposure of medical staff.

Robotic endoscope-automated via laryngeal imaging for tracheal intubation has been developed to enable automated tracheal intubation [13]. The robotic device has real-time image recognition and remote automatic positioning function. The user can manually control the bending and movement of the endoscope tip; when the image recognition detects the glottal opening, the user can press a dedicated button to activate the automatic mode. In automatic mode, the tip of the speculum moves toward the geometric center point of the glottal opening until it entered the trachea. The robotic endoscope-automated via laryngeal imaging for tracheal intubation was successfully performed for the first time on a manikin and obtained comparable results in a convenience sample of anesthetists and lay participants with no medical training. This study suggests that the time required for non-trained participants to master the skill is similar to that of an experienced anesthesiologist, which may help inexperienced healthcare workers to perform tracheal intubation. However, all the intubations were performed on the airway trainer mannequin, not yet in clinical practice.

Prolonged mechanical ventilation (PMV) is commonly defined as more than 21 days; however, substantial variation exists in the terminology and definitional criteria for PMV [14]. Early identification of critically ill patients requiring PMV has proven to be difficult. AI can help quantify the risk of extubation, thus helping to personalize and achieve accurate extubation. In a study that defined the duration of ventilation with >7 days as PMV, 20,262 total hospital stays with mechanical ventilation were identified from the Multiparameter Intelligent Monitoring in Intensive Care III [15]. Patients requiring tracheostomy placement were identified by the presence of ICD-9-CM procedure codes (31.1, 31.29). Machine-learning classifiers were created using a gradient-boosted decision tree algorithm based on the outcomes of PMV and tracheostomy placement. It showed that variables with the higher importance for predicting PMV and tracheostomy were the logistic organ dysfunction score (pulmonary component), the sepsis-related organ failure assessment score, cardiac arrhythmia, the Oxford acute severity of illness score before ICU stay. The classifiers predicted PMV for these patients who were admitted to surgical ICU with an AUC of 0.852, significantly reducing the probability of reintubation in patients.

Ultrasound-guided anesthetic techniques

For ultrasound-guided anesthetic techniques, artifacts, noise, and anatomic structure variability all affect the accuracy of nerve tracking and needle positioning. AI could be used to assist ultrasound-guided local anesthetic operations.

In nerve block anesthesia, the block performance varies due to the location, image parameters and patient specificity during the actual scanning. Compared with the traditional feature extraction method, DL neural network is more stable and accurate. In 2013, the first robotic system, Magellan, was invented to perform nerve blocks using a remote-control center [16]. The researchers presented the first human test of a robotic ultrasound-guided nerve block system, and the success rate was 100%.

Right after that, to prove whether this newly invented system can shorten the operator learning curve, Morse et al. compared success rates, learning curves, performance times, and inter-subject performance variability between robot-assisted and manual ultrasound-guided nerve block [17]. Analysis of variance indicated that there were significant differences in performance times for performing the manual blocks; no statistical difference for the robot-assisted blocks and linear regression indicated that the average shortening time between two consecutive trials of robot-assisted nerve blocks was significantly longer than that of manual blocks [(1.8 ± 1.6) seconds vs (0.3 ± 0.3) seconds]. Therefore, this robot-assisted model can help beginners master the operation skills faster and reduce the operator interval differences [17].

At present, epidural puncture needle placement is mainly performed manually that largely depending on the hand feel with a very high failure rate. Moreover, improper placement of the epidural needle can lead to inadequate anesthesia, post-puncture headaches and other potential complications. Ultrasonography for neuraxial anesthesia is increasingly being used to identify spinal structures and localize correct point of needle insertion to improve procedural success. Pesteie et al. used the hybrid ML system to automatically localize the insertion point of epidural needle placement and identify anatomical landmarks of epidural space in ultrasound images [18]. Compared with sonographers, the hybrid machine ML has a transverse and longitudinal error of 1 mm and 0.4 mm in the 3D-augmented test data plane, which effectively reduces the error and improves the comfort and safety of patients.

Performing subarachnoid or epidural anesthesia in obese patients, especially in obese pregnant women, remains a challenging task, as obesity and pregnancy may cause spinal changes, which in turn increases operational difficulty of determining the needle insertion point. Acting on ultrasound imaging of the lumbar spine, a program based on ML algorithms was developed to automatically identify the needle insertion site, and the first attempt success rate for spinal anesthesia was 79.1% [19]. This shows that the automated spinal landmark identification program is able to provide assistance to needle insertion point identification in obese patients.

For practicing the ultrasound-guided regional anaesthesia (UGRA), the tracking of the nerve structure in ultrasound images is extremely labor intensive, even for experienced operators, due to the noise and other artifacts. By using additional information to track nerves and blood vessels, the combination of a detection and tracking framework and a robotic system can assist with UGRA. A new and robust tracking technique by using Adaptive Median Binary Pattern was introduced as texture feature for tracking algorithms. This fully automatic nerve tracking method in ultrasound images achieved best performance with 95% accuracy when it was applied in real data and evaluated in different situations [20].

Studies of stroke require the acquisition of patient-specific geometry of the carotid artery bifurcation. Although C-mode CT and magnetic resonance are effective tests, there are many limitations including but not limited to ionizing radiation, unaffordable expense, and not available for all patients. De Ruijter et al. developed an automatic 3D geometry segmentation algorithm for ultrasound images using a 2D ultrasound probe [21]. This algorithm is able to segment the common carotid artery, the internal carotid artery, and the external carotid artery including the carotid bifurcation in transverse B-mode images in both healthy and diseased arteries. The quality metrics of the method performed significantly better than or similar to those proposed in the previous papers, however, this method was tested on limited data, 19 healthy volunteers and 3 patients, which needs further validation [21].

Depth of anesthesia (DoA) monitoring

BIS and electroencephalogram (EEG) characteristic parameters are usually used to evaluate DoA. However, in anesthesia monitoring, the reliability of BIS can be affected by numerous interferences, including patient factors (basic diseases, etc.), different anesthetics, muscle relaxants, intraoperative electric coagulation etc. [22]. AI could be used to refine DoA monitoring. Yu et al. proposed an adaptive control scheme that combines BIS and blood pressure to ensure the proper dosage of drugs to achieve target setting point even if BIS signal is lost intermittently [23].

The competence of processing complex data streams, such as EEG, using ML methods have been testified. A range of EEG-based signals indicating brain states have been analyzed by ML approaches to accurately scale the DoA. In Gu's research, an algorithm based on artificial neural networks and EEG to evaluate DoA was presented, and the output results of this algorithm

Table 1. Anesthesia delivery control system

Name	Control system	Characteristics
Target controlled infusion system	Open-loop system	Based on pharmacokinetic models of drugs to achieve specific plasma drug levels. The concentration of the drug needs to be manually determined and adjusted.
Single input single output system	Closed-loop systems	1. Bispectral index -guided autonomous system. 2. Real-time monitoring of anesthesia parameters (e.g. Bispectral index, blood pressure, and oximetry) as feed back for drug infusion. 3. Algorithms, such as reinforcement learning, neural net work, and fuzzy logic, can improve the performance of the system [3].
Multiple input multiple output system	Closed-loop systems	1. Real-time monitoring hypnosis, analgesia, and muscle relaxation simultaneously as feedbacks for drug infusion. 2. Algorithms, such as reinforcement learning, neural net work, and fuzzy logic, can improve the performance of the system [3].

clearly demonstrated a strong linear correlation with BIS [24].

Moreover, ML is used to distinguish states of consciousness based on EEG [25]. Three sedation situations were studied with dexmedetomidine i.v., propofol i.v., or natural sleep in this research. Distinct source localized signatures of sensory disconnection and unconsciousness were identified using support vector machine classification, indicating that occipital delta power could differentiate disconnected and unconscious states for dexmedetomidine but not for sleep/propofol. These findings may enable novel anesthetic state monitoring to distinguish between sensory disconnection and unconsciousness, and may provide novel insights into the biology of arousal.

With the deepening of DoA investigation, attention has been gradually paid to other clinical signals as well, for example, mid-latency auditory evoked potentials, end-tidal carbon dioxide, blood pressure, and heart rate [26, 27].

Intraoperative hypotension and hypoxemia prediction

Intraoperative monitoring of adverse events, such as intraoperative hypotension, which is commonly encountered, is crucial in anesthesia management. Early prediction of adverse events allows physicians to take timely action to reduce patient morbidity and mortality. As mentioned earlier, due to the datafication of clinical information, real analysis based on big data is an advantage of AI for predicting patterns of intraoperative blood pressure [28]. Hatib et al. established a model for predicting hypotension based on the analysis of arterial pressure waveforms using ML methods [29]. In this real-time dynamic prediction system, the evolution of mean arterial pressure, the time-to-event interval, is highly consistent with the hypotension prediction index (the algorithm output) [29].

Similarly, there is a lack of reliable indicators for the prevention of intraoperative hypoxemia. A ML-based system by visually presenting a weighted function model, was developed to assist anesthesiologist in predicting the occurrence of hypoxemia during anesthesia and delineate the risk factors that contributed to the prediction [30].

Closed loop anesthesia control system

In the field of anesthesiology, how to achieve perioperative precise drug delivery and reduce the workload of anesthesiologists has always been concerned. Therefore, drug delivery robots have been rapidly developed and widely used in clinical practice. These major advances in anesthesia delivery control system are summarized in **Table 1**.

In 2016, an intravenous anesthesia robot developed by a Beijing company was successfully tested for the first time in Beijing and relevant research papers of its mature core technologies have been published before the system came out [31-34]. The system is used to automatically complete general anesthesia mainly through continuous monitoring of the depth of sedation, pain index, muscle relaxation, blood flow and other parameters, and then remote control through cloud computing to adjust the rate of drug delivery with feedback. At present, the system is in the stage of clinical testing, which opens a precedent for the application of Multiple Input Multiple Output systems [35].

Pattern recognition capabilities of neural networks enable the automatic classification of breath failures. Many studies on intelligent anesthesia alarm systems have shown that neural networks are the technical cornerstone in this

field [36]. In 1994, Orr et al. installed sensors at designated locations to measure respiratory signals, such as pressure, flow, and carbon dioxide, among which 30 descriptive features were extracted for each breath circuit, and finally, a neural network system was trained to identify 13 faults in an anesthesia breathing circuit [37]. In animal tests, the system detected 95.0% and 86.9% of the introduced failures in controlled ventilation and spontaneous respiration, respectively [37].

Similarly, a hierarchical artificial neural network monitor developed by Narus et al. identified 23 faults in 92% of cases and 21 faults in 83% of cases during controlled and spontaneous breathing, respectively [38]. These days, artificial neural networks have been proven be useful in creating intelligent anesthesia alarm systems and have already been applied to some high-end ventilators or anesthesia machines.

In recent years, closed-loop systems have not been limited to anesthesia, sedation, analgesia, muscle relaxation, etc. In order to further explore the clinical value of closed-loop systems, researchers have also developed closed-loop systems for perioperative fluid infusion and vasoactive drug management. In the treatment of acute respiratory distress syndrome, positive end expiratory pressure (PEEP) is one of the important parameters following the principles of the open lung concept [39]. Application of PEEP can reinflate collapsed alveoli and increase arterial oxygen content, but too high PEEP can lead to hemodynamic instability and reduce oxygen delivery. AI can be used to develop an automatic control system for mechanical ventilation therapy based on the open lung concept. This innovative closed-loop mechanical ventilation system intelligently regulates intraoperative PEEP, end-tidal carbon dioxide, and other parameters, as well as the use of vasoactive drugs, leading to a significant improvement in oxygenation. The experiment with porcine dynamics demonstrated the feasibility and usefulness of this automatic closed-loop ventilation therapy, with hemodynamic control for severe acute respiratory distress syndrome [39].

AI in post-operative anesthesia

Pain treatment

In the field of pain treatment, the use of pain questionnaires is subjective and limited. Thanks to its powerful data analytics, AI is turning out to be valuable. Hu et al. presented an innovative and feasible neuroimaging-based augmented reality/AI concept that can potentially transform the human brain into an objective target to visualize and precisely measure and localize pain in real time [40]. In this study, the neutral network with 3 layers achieved an optimal classification accuracy of 80.37% in discriminating pain and no-pain, and the neural networks with 6 layers achieved the highest classification accuracy of 74.23% for localizing left side pain, right side pain, and no-pain states [40].

Postoperative complication prediction

As described above, postoperative adverse events for hospitalized patients can be better predicted with preoperative risk prediction, intraoperative hypotension prediction, and intraoperative hypoxemia prediction.

Postoperative in-hospital mortality prediction

An important evaluation in post anesthesia care unit is to assess post-surgical in-hospital mortality. In this context, Lee et al. developed a generalized additive model with neural networks [41]. It turns out that in terms of performance, it exhibited a high AUC in predicting the mortality of patients with general anesthesia. Over relatively simple models such as Logistic Regression, it shows better model performance; while over relatively complicated models such as DL, it shows less “black box” features [41]. For example, it can work on nonlinear data, and it has better transparency and higher accuracy with a notable AUC of 0.921.

Perioperative deep venous thrombosis (DVT) prediction

The formation of DVT is an extremely complex pathological process, and studies have shown that it is closely related to numerous basic health data and surgical factors of patients [42]. Any single factor is not enough to directly lead to the occurrence of DVT, so predicting DVT based on one or few variables is bound to increase the rate of missed diagnosis [42]. A patient-specific decision system, which had its origin from 35,963 total hip and knee arthroplasty patients, was created to predict the incidence of DVT, pulmonary emboli and major bleeding after operation [43].

Summary and future directions

The application of AI in medicine is aimed at solving patients’ health problems and has grown rapidly in recent years. AI is a potentially powerful tool, but it comes with multiple chal-

lenges [44]. One objection is that AI, especially neural networks, has the black box problem. The physician can provide the input and get the prediction (output) through an algorithmic model but cannot examine the logic that produced the decision. In other words, the model cannot give extra details to explain how it works and why the output is produced [2]. Therefore, people pay attention to transparency and interpretability of the AI algorithms. For example, decision tree is an easy to understand and interpretable model, because it not only gives the prediction of the input data, but also provides a series of intermediate decisions that lead to the final prediction, which the researcher can verify or question. However, the accuracy of decision tree prediction is lagging behind that of neural networks. Therefore, combining neural networks with decision trees is a feasible direction to improve their interpretability and maintain their accuracy.

Secondly, AI algorithms are susceptible to bias in data. Whether human biases, like racial biases, will be coded explicitly or implicitly into the algorithms is debatable. People generally believe that ML algorithms, without judgments of human, is free of bias, but in fact bias is horrendously integrated into sample data. The main cause of ML data bias is the lack of diversity of data samples [45]. Data from a single source may lead to erroneous conclusions.

The promise of a fiduciary relationship between patients and doctors becomes unclear with the involvement of AI [46]. At present, with the introduction of AI, there are no laws and regulations to clarify the fiduciary compact. Who is responsible for the errors that generated by AI during its application in diagnoses? Is the responsibility for determining treatment still with the physician?

Doctors are aware of protection of patient privacy, but AI requires all aspects of the patient's data, because patients cannot benefit from the algorithm without data. The implementation of AI will therefore require a redefinition of confidentiality and other core tenets of professional ethics [46]. At the intersection of AI and medicine, a strong regulatory body is urgently needed to weigh all the elements of data ethics management [3]. The use of scientific regulatory concepts holds the potential to foster a deep integration among AI, the medical field, and regulators [47].

Will anesthetists be replaced by AI and lose their jobs and have to deliver food [48]? Maybe in the future, but not yet. Now we are in the "weak AI" stage where AI can achieve good results in a specific domain, but not as universal as people [49]. For example, AlphaGo can only be used in Go, not in chess or military chess. Similarly, the model developed by Lee et al. seems be incapable of predicting outcomes if we double the dose of either propofol or remifentanil, because the training data did not include this case when the neural network was built [22].

Admittedly, AI is technologically superior to humans in integrating complex, large, and structured data sets. But most of the data that doctors collected is based on a trusted doctor-patient relationship, wherein patients place their trust in their healthcare providers rather than AI [2]. Therefore, physicians should not only make full use of the powerful DL capabilities of AI, but also give full play to the advantages of humans, striving for a complementary relationship between humans and computers.

References

[1] Maheshwari K, Cywinski JB, Papay F, et al. Artificial Intelligence for Perioperative Medicine: Perioperative Intelligence. Anesth analg 2023;136:637-645.

[2] Hashimoto DA, Witkowski E, Gao L, et al. Artificial Intelligence in Anesthesiology: Current Techniques, Clinical Applications, and Limitations. Anesthesiology 2020;132:379-394.

[3] Singh M, Nath G. Artificial intelligence and anesthesia: A narrative review. Saudi J Anaesth 2022;16:86-93.

[4] LeCun Y, Bengio Y, Hinton G. Deep learning. Nature 2015;521:436-444.

[5] Zhang L, Fabbri D, Lasko TA, et al. A System for Automated Determination of Perioperative Patient Acuity. J Med Syst 2018;42:123.

[6] Bihorac A, Ozrazgat-Baslanti T, Ebadi A, et al. MySurgeryRisk: Development and Validation of a Machine-learning Risk Algorithm for Major Complications and Death After Surgery. Ann Surg 2019;269:652-662.

[7] Fritz BA, Cui Z, Zhang M, et al. Deep-learning model for predicting 30-day postoperative mortality. Brit J Anaesth 2019;123:688-695.

[8] Hayasaka T, Kawano K, Kurihara K, et al. Creation of an artificial intelligence model for intubation difficulty classification by deep learning (convolutional neural network) using face images: an observational study. J Intensive Care 2021;9:38.

[9] Matava C, Pankiv E, Ahumada L, et al. Artificial intelligence, machine learning and the pediatric airway. Pediatr Anesth 2020;30:264-268.

[10] Xia M, Cao S, Zhou R, et al. Acoustic features as novel predictors of difficult laryngoscopy in orthognathic surgery: an observational study. Ann Transl Med 2021;9:1466.
[11] Hemmerling TM, Taddei R, Wehbe M, et al. First robotic tracheal intubations in humans using the Kepler intubation system. Brit J Anaesth 2012;108:1011-1016.
[12] Wang R, Zhang Q, Ding H, et al. Design and Feasibility Study of Tracheal Intubation Device Based on Magnetic Navigation Technology. Chin J Med Instrum 2021;45:22-25.
[13] Biro P, Hofmann P, Gage D, et al. Automated tracheal intubation in an airway manikin using a robotic endoscope: a proof of concept study. Anaesthesia 2020;75:881-886.
[14] Rose L, McGinlay M, Amin R, et al. Variation in Definition of Prolonged Mechanical Ventilation. Respiratory Care 2017;62:1324-1332.
[15] Parreco J, Hidalgo A, Parks JJ, et al. Using artificial intelligence to predict prolonged mechanical ventilation and tracheostomy placement. J Surg Res 2018;228:179-187.
[16] Hemmerling TM, Taddei R, Wehbe M, et al. Technical communication: First robotic ultrasound-guided nerve blocks in humans using the Magellan system. Anesth Analg 2013;116:491-494.
[17] Morse J, Terrasini N, Wehbe M, et al. Comparison of success rates, learning curves, and inter-subject performance variability of robot-assisted and manual ultrasound-guided nerve block needle guidance in simulation. Brit J Anaesth 2014;112:1092-1097.
[18] Pesteie M, Lessoway V, Abolmaesumi P, et al. Automatic Localization of the Needle Target for Ultrasound-Guided Epidural Injections. IEEE T Med Imaging 2018;37:81-92.
[19] In Chan JJ, Ma J, Leng Y, et al. Machine learning approach to needle insertion site identification for spinal anesthesia in obese patients. BMC Anesthesiol 2021;21:246.
[20] Alkhatib M, Hafiane A, Tahri O, et al. Adaptive median binary patterns for fully automatic nerves tracking in ultrasound images. Comput Meth Prog Bio 2018;160:129-140.
[21] De Ruijter J, van Sambeek M, van de Vosse F, et al. Automated 3D geometry segmentation of the healthy and disea-sed carotid artery in free-hand, probe tracked ultrasound images. Med Phys 2020;47:1034-1047.
[22] Lee HC, Ryu HG, Chung EJ, et al. Prediction of Bispectral Index during Target-controlled Infusion of Propofol and Remifentanil: A Deep Learning Approach. Anesthesiology 2018;128:492-501.
[23] Yu YN, Doctor F, Fan SZ, et al. An Adaptive Monitoring Scheme for Automatic Control of Anaesthesia in dynamic surgical environments based on Bispectral Index and Blood Pressure. J Med Syst 2018;42:95.
[24] Gu Y, Liang Z, Hagihira S. Use of Multiple EEG Features and Artificial Neural Network to Monitor the Depth of Anesthesia. Sensors (Basel) 2019; 19:null.
[25] Casey CP, Tanabe S, Farahbakhsh Z, et al. Distinct EEG signatures differentiate unconsciousness and disconnection during anaesthesia and sleep. Brit J Anaesth 2022;128:1006-1018.
[26] Nagaraj SB, Biswal S, Boyle EJ, et al. Patient-Specific Classification of ICU Sedation Levels From Heart Rate Variability. Crit Care Med 2017; 45:e683-e690.
[27] Ranta SO, Hynynen M, Räsänen J. Application of artificial neural networks as an indicator of awareness with recall during general anaesthesia. J Clin Monit Comput 2002;17:53-60.
[28] Alexander JC, Romito BT, Çobanoğlu MC. The present and future role of artificial intelligence and machine learning in anesthesiology. Int Anesthesiol Clin 2020;58:7-16.
[29] Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. Anesthesiology 2018;129:663-674.
[30] Lundberg SM, Nair B, Vavilala MS, et al. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. Nat Biomed Eng 2018;2:749-760.
[31] Zhang JW, Lv ZG, Kong Y, et al. Wavelet and pain rating index for inhalation anesthesia: A randomized controlled trial. World J Clin Cases 2020;8:5221-5234.
[32] Wu L, Wang S, Wang Y, et al. Prediction of Hemodynamic Reactivity by Electroencephalographically Derived Pain Threshold Index in Children Undergoing General Anesthesia: A Prospective Observational Study. J Pain Res 2019;12:3245-3255.
[33] Wang R, Deng Y, Zhou S, et al. EEG-derived pain threshold index for prediction of postoperative pain in patients undergoing laparoscopic ur-ological surgery: a comparison with surgical pleth index. J Clin Monit Comput 2021;35:1395-1402.
[34] An JX, Wang Y, Cope DK, et al. Quantitative Evaluation of Pain with Pain Index Extracted from Electro-encephalogram. Chinese Med J-Peking 2017;130:1926-1931.
[35] Fu HL, Yuan HB. Yesterday, today and tomorrow of robotic anesthesia. Shanghai Med J 2022;45:146-148.
[36] Vellido A, Ribas V, Morales C, et al. Machine learning in critical care: state-of-the-art and a sepsis case study. Biomed Eng Online

2018;17:135.
[37] Orr JA, Westenskow DR. A breathing circuit alarm system based on neural networks. J Clin Monitor 1994;10:101-109.
[38] Narus SP, Kück K, Westenskow DR. Intelligent monitor for an anesthesia breathing circuit. Proc Annu Symp Comput Appl Med Care 1995;96-100.
[39] Pomprapa A, Muanghong D, Köny M, et al. Artificial intelligence for closed-loop ventilation therapy with hemodynamic control using the open lung concept. Int. J. Intell. Comput Cybern 2015;8:50-68.
[40] Hu XS, Nascimento TD, Bender MC, et al. Feasibility of a Real-Time Clinical Augmented Reality and Artificial Intelli-gence Framework for Pain Detection and Localization From the Brain. J Med Internet Res 2019;21:e13594.
[41] Lee CK, Samad M, Hofer I, et al. Development and validation of an inter-pretable neural network for prediction of postoperative in-hospital mortality. NPJ Digit Med 2021;4:8.
[42] Januel JM, Chen G, Ruffieux C, et al. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review. JAMA-J Am Med Assoc 2012;307:294-303.
[43] Shohat N, Ludwick L, Sherman MB, et al. Using machine learning to predict venous thromboembolism and major bleeding events following total joint arthroplasty. Sci Rep 2023;13:2197.
[44] Quinn TP, Senadeera M, Jacobs S, et al. Trust and medical AI: the challenges we face and the expertise needed to overcome them. J Am Med Inform Assoc 2021;28:890-894.
[45] Keyes KM, Westreich D. UK Biobank, big data, and the consequences of non-representativeness. Lancet 2019; 393:1297.
[46] Char DS, Shah NH, Magnus D. Implementing Machine Learning in Health Care - Addressing Ethical Challenges. New Engl J Med 2018;378:981-983.
[47] Lennerz JK, Green U, Williamson DFK, et al. A unifying force for the realization of medical AI. NPJ Digit Med 2022;5:172.
[48] Gambus P, Shafer SL. Artificial Intelligence for Everyone. Anesthesiology 2018;128:431-433.
[49] Scerri M, Grech V. Artificial intelligence in medicine. Early hum dev 2020; 145:105017.

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Research progress of oxidative stress in sepsis-associated liver injury

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Highlights

- The approaches of antioxidant therapy to alleviate sepsis-associated liver injury are summarized from the perspective of oxidative stress in different cells of the liver.
- Reactive oxygen species, one of the main substances that induce oxidative stress, affects the molecular mechanism of the relevant signaling pathways.
- Antioxidant therapy is helpful for the recovery of various liver cells in sepsis-associated liver injury and is expected to advance basic and clinical research.

Abstract

Sepsis is a systemic inflammatory response that caused by infection or trauma, often resulting in multiple organ dysfunction. Its mortality rate is relatively high, ranging between 54% and 68%, and ineffective treatment and poor prognosis pose significant challenges to healthcare in recent years. One of the main pathogeneses of sepsis-induced liver injury is oxidative stress (OS), which refers to a state where the antioxidant system cannot balance oxidative products, leading to the accumulation of excessive oxidative products in the body. When sepsis occurs, the amount of reactive oxygen species produced by the body increases far beyond the levels that can be scavenged by the antioxidant system, thus damaging liver cells and aggravating liver damage. This article introduces the oxidative/antioxidant system, oxidative stress-related pathways, and the molecular mechanism of OS in various types of hepatocytes, with emphasis on the antioxidant treatment on different hepatocytes, in order to understand the mechanism of OS involved in the development and progression of sepsis-associated liver injury. As the research deepens, improving liver function through the treatment of different cells and facilitating related clinical research are expected to provide a new target pathway for the treatment of sepsis-associated liver injury.

Keywords: Sepsis-associated liver injury, liver injury, oxidative stress, reactive oxygen species

Introduction

Sepsis is a systemic inflammatory response caused by infection, trauma, and other factors, resulting in multi-organ dysfunction. In severe cases, it can progress to life-threatening septic shock and organ failure [1, 2]. Sepsis mainly induces liver injury, lung injury, cardiac dysfunction, gastrointestinal injury, and kidney injury. Among them, the liver is the most important detoxification and metabolic organ of the human body, and it is very susceptible to infection and damage. Previous studies have shown that the reasons for the pathogenesis of sepsis-associated liver injury include oxidative stress (OS), hepatic microcirculation disorders, energy metabolism disorders, inflammatory response, etc. [3-5]. When sepsis occurs, the main mechanism of liver injury is OS due to increased oxygen free radicals and peroxidation of lipids

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in the body [6]. Based on a review of recent literature, this paper summarizes the mechanism of OS-induced liver injury in sepsis, and the signaling pathways of reactive oxygen species (ROS) in sepsis-associated liver injury, as well as the effects of ROS on hepatocyte injury and antioxidant therapy.

Review progress

Oxidative stress

Oxidative damage

OS is a state of imbalance between oxidant and antioxidant in the body. When ROS and reactive nitrogen species such as nitric oxide (NO) increase in large quantities, the absence/shortage of antioxidants disrupts the balance in the body [7, 8]. ROS refers to oxygen free radicals and non-free radicals produced by the body, mainly containing the substrates of the respiratory chain of the inner mitochondrial membrane, such as O^{2-}, HO^{-} and H_2O_2, with oxidizing ability and toxic effects on most cells [9]. In a physiological state, as a by-product of the oxidation system, the production and clearance of ROS are in dynamic equilibrium in the body. Additionally, the level of ROS rises and exceeds the body's clearance ability, which can increase lipid peroxidation in related tissues, leading to abnormal expression of related proteins, DNA damage, and gene mutation [10]. Malondialdehyde (MDA), a lipid free radical, is the principal degradation product of lipid peroxides, which can damage mitochondrial and cell membranes, thereby inhibiting the function of membrane proteins, impairing the structural integrity of mitochondria, and leading to cell damage [10]. At the same time, NO synthase is greatly augmented, and NO can restrain the binding of mitochondrial cytochrome C to O_2, leading to mitochondrial dysfunction. Thus, damage to cellular mitochondria causes spillover of cytochrome C from mitochondria into the cytoplasm, contributing to apoptosis [11, 12]. Through a series of reactions, it eventually contributes to autophagy, necrosis, and apoptosis, etc.

Anti-oxidation system

The antioxidant system is composed of endogenous molecules, including both enzymes and non-enzymes. The main enzymes include superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT). To put it more precisely, SOD is an important antioxidant enzyme mainly involved in scavenging oxygen radicals. When ROS increases, SOD reacts with O^{2-} to produce H_2O_2, which is then converted into water by CAT and GSH-Px to remove ROS and protect cells from damage [13]. In contrast, when the contents of CAT, GSH-Px and SOD increase, the ROS and the MDA in the body reduce. The non-enzymes include vitamin C, vitamin E, uric acid, metal-binding protein, polyamines, bilirubin, carotenoids, etc. [14].

OS-related signaling pathways

Nuclear erythrocytes 2-related factor (Nrf2) signaling pathway

Nrf2 is a key factor in cellular oxidative stress and is negatively regulated by cytoplasmic Kelch-like ECH-associated protein 1 (Keap1) [15]. Under normal physiological conditions, Keap1 is a substrate linker protein of the Cullin3 (Cul3)-dependent E3 ubiquitin ligase complex. Keap1 contains three functional domains, a Broad-complex, Tramtrack, and Bric-à-brac (BTB) domain, an intervening region domain, and a Kelch or double-glycine repeat domain. Wherein, BTB domain binds to Cul3 to assemble into a functional E3 ubiquitin ligase complex (Keap1-Cul3-E3). Keap1-Cul3-E3 ubiquitin ligase targets the Neh2 domain located at the N-terminus of Nrf2 and promotes Nrf2 ubiquitination [16]. After that, ubiquitinated Nrf2 is delivered to the 26S proteasome for degradation.

When the body is in an OS state, ROS modifies specific cysteine residues in Keap1, causing conformational changes in Keap1-Cul3-E3 ubiquitin ligase and interfering with Nrf2 ubiquitination [17]. Alternatively, it facilitates the breakdown of Nrf2 with Keap1 by activating protein kinase C. Nrf2 is then transferred into the nucleus by oxidative stressors such as electrophiles and binds to the antioxidant response element (ARE) by heterodimerization with the small Maf transcription factors [18]. Subsequently, the Nrf2-ARE signaling pathway initiates and promotes the expression of antioxidant enzyme genes, such as CAT, SOD, GSH-Px, glutathione S-transferase, NADH quinone oxidoreductase 1, and heme oxygenase 1, which in turn provides antioxidant defense [19, 20]. Moreover, ROS activates glycogen synthase kinase 3, nucleating phosphorylated Nrf2 and Keap1 and affecting the degradation of Nrf2 (**Figure 1**) [21]. In general, ROS can promote Nrf2 into the nucleus through various ways, and then activate its downstream pathway.

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway

NF-κB is a transcription factor protein that con-

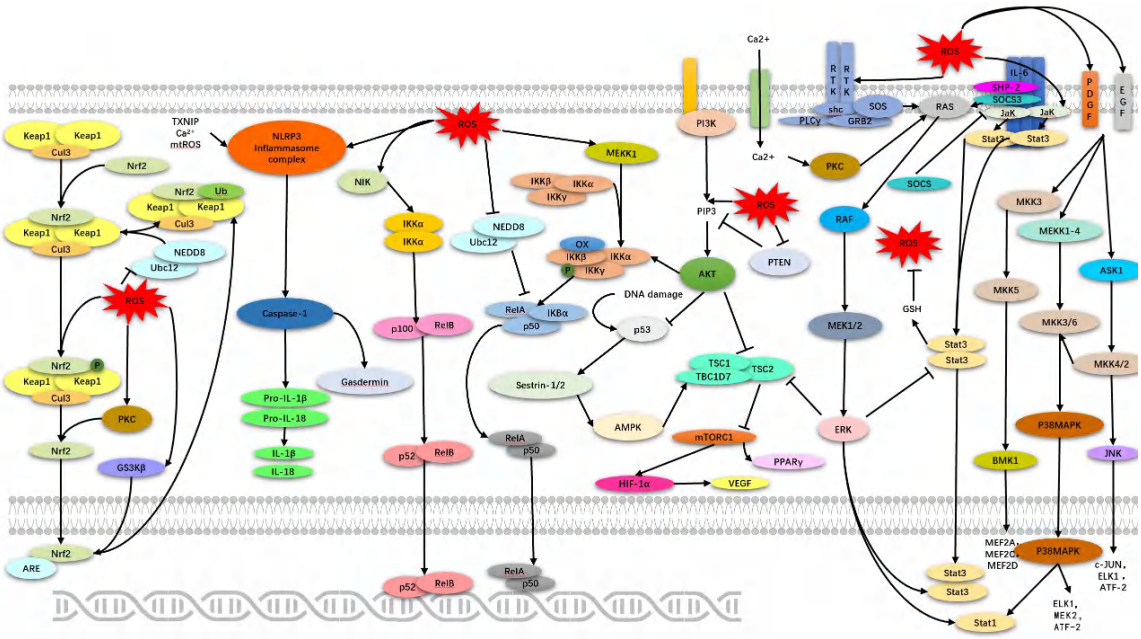

Figure 1. Effects of ROS on different signaling pathways. ROS, reactive oxygen species; Keap1, Kelch-like ECH-associated protein 1; Cul3, Cullin3; Nrf2, Nuclear erythrocytes 2-related factor; ARE, antioxidant response element; Ubc, E2-ubiquitin conjugating enzyme; NEDD8, neural precursor cell expressed developmentally downregulated 8; NLRP3, Nucleotide-binding oligomerization domain-like receptor protein 3; NIK, Nuclear factor kappa-light-chain-enhancer of activated B cells inducing kinase; IKK, IκB kinase; MEKK1, mitogen-activated protein kinase kinase kinase 1; AMPK, adenosine 5'-monophosphate-activated protein kinase; PI3K, Phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol 3, 4, 5-triphosphate; AKT, activate protein kinase B; TSC, tuberous sclerosis complex (consisting ofTSC1, TSC2, TBC1D7); VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; shc, recombinant protein; GRB, growth factor receptor-bound protein; SOS, son of sevenless; PLCγ, specific phospholipase Cγ; STAT; Signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; SHP-2, Src homology 2 domain-containing protein tyrosine phosphatase; JAK, janus kinase; MAPK, Mitogen-activated protein kinase; MEF2, myocyte enhancer factor 2 (contain: MEF2A, MEF2C, MEF2D); ELK1, ETS transcription factor; ATF-2, activating transcription factor 2; ERK, extracellular signal-regulated kinase; ASK1, apoptosis signal-regulating kinase 1; PDGF, platelet-derived growth factor; JNK, c-Jun N-terminal kinase; PPAR, Peroxisome proliferator-activated receptor; HIF-1α, hypoxia-inducible factor-1 alpha; TXNIP, Thioredoxin-interacting protein; GSH, glutathione; PKC, protein kinase C; Raf, rapidly accelerated fibrosarcoma; OX, oxide. ⟶ : activation; —I: inhibition.

tains five different family proteins: Rel A (p65), Rel B, c-el, p105 (p50 precursor/NF-κB1), and p100 (p52 precursor/ NF-κB2), by forming homologous or heterologous dimers with the DNA-binding protein -Rel [22]. NF-κB is regulated by proteins of the IκBs family, including IκBα, IκBβ, IκBγ, IκBε, and B cell leukemia-3. In a physiological state, NF-κB is inactivated in the cytoplasm due to its binding with IκBα [23]. NF-κB activation occurs through two major signaling pathways: canonical and non-canonical NF-κB signaling pathways. The canonical pathway refers to the activation of IκB kinase (IKK) and subsequent phosphorylation of IκBα. IκBα in the complex dissociates from NF-κB1, activating NF-κB1 [24]. The non-canonical NF-κB pathway refers to NF-κB inducing kinase activation and subsequent phosphorylation of IKKα. IKKα phosphorylates p100 to degrade to p52 [25]. Following this, the combination of Rel B and p52 translocates to the nucleus to regulate gene transcription [26].

During OS, ROS mainly affects the activation of NF-κB by activating phosphorylation of IκBα and adjusting the mitogen-activated protein kinase kinase kinase 1 (MEKK1) upstream of IKK [27-29]. ROS can also interfere with ubiquitination and degradation of IκB by inactivating Ubc12, thereby impacting the activation of NF-κB [30]. In the non-canonical pathway, ROS could activate NF-κB2 by upregulating NF-κB inducing kinase (**Figure 1**) [31].

Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) signaling pathway

NLRP3 can form NLRP3 inflammasome bodies with precursors of apoptosis-associated spot-like protein in the caspase recruitment domain and cysteinyl aspartate specific proteinase 1 (Caspase-1). NLRP3 inflammasome is a

multi-protein macromolecular complex that processes Pro Caspase-1 into bioactive Caspase-1, cuts Gasdermin protein to cause cell perforation and mediates interleukin (IL) 1β- and IL-18-related responses.

With the invasion of pathogen-associated molecular patterns or damage associated molecular patterns, mitochondria are stimulated to produce ROS. ROS activates NLRP3 inflammasomes or reacts with thioredoxin interaction, which then releases thioededoxin and activates NLRP3 inflammasomes (**Figure 1**) [32].

Mitogen-activated protein kinase (MAPK) signaling pathway

The cascade of MAPK consists of four main components: extracellular signal-associated kinase (ERK1/2), c-Jun N-terminal kinase, p38 kinase (p38), and large mitogen-activated protein (MAP) kinase 1 (BMK1/ERK5) [33]. MAP kinase kinase kinase (MAPKKK/MEKK/MKK) is activated, which then phosphorylates and activates MAP kinase kinase (MAPKK/MEK/MKK). Phosphorylation of MAPKK activates MAP kinase (MAPK), which, in turn, phosphorylates various substrate proteins [34].

ROS can activate receptors of epidermal growth factor and platelet-derived growth factor, activating Ras on cell membranes. Ras then recruits rapidly accelerated fibrosarcoma (Raf) (MAPKKK) in cytoplasm into the cell membrane for activation [35]. Activated Raf phosphorylates MEK1/2(MAPKK), which then results in ERK activation [36]. ROS acts on thioededoxin and glutaraldehyde, dissociating them from MAPKKKs such as apoptosis signal-regulating kinase 1 and MEKK1-4 [37]. This activation of MAPKKKs leads to the activation of MAPKK, subsequently activating c-Jun N-terminal kinase, p38, and BMK1 (**Figure 1**).

Phosphatidylinositol 3-kinase (PI3K) signaling pathway

PI3K catalyzes the synthesis of phosphatidylinositol 3, 4, 5-triphosphate to recruit and activate protein kinase B (AKT). Furthermore, it promotes the activation and transcription of Sestrins, endothelial nitric oxide synthase, forkhead box protein O, mechanistic target of rapamycin 1, and p53.

ROS can not only activate PI3K and its downstream signaling pathways, but also inactivate phosphatase and tensin homolog (PTEN) and inhibit AKT activation by negatively regulating phosphatidylinositol 3, 4, 5-triphosphate. Its downstream pathway, Sestrins, comprises stress response proteins crucial for cellular adaptation to OS. Sestrins play a significant role in enhancing the body's tolerance to OS, preventing the accumulation of ROS and MDA through its inherent antioxidant activity and the regeneration of thiol peroxidase (peroxiredoxin) [38, 39]. Sestrin2 also inhibits sepsis-associated liver injury by activating the transcription factors p53, Nrf2, and hypoxia-inducible factor-1α [40]. The other downstream pathway, mTOR, is a class of serine/threonine kinases that affect the OS of the body by regulating hypoxia-inducible factor-1α, peroxisome proliferators-activated receptors-γ and other pathways (**Figure 1**).

Signal transducer and activator of transcription (STAT) signaling pathway

STAT, including STAT1-4, STAT5 (STAT5A and STAT5B), and STAT6, is also an important protein for OS. When IL-6 and other cytokines bind to the relevant receptors, they can change the molecular conformation of the receptor [41]. The coupled Janus kinase (JAK) kinases approach each other and phosphorylate tyrosine to activate the JAK kinases. The activated JAK kinases allow the corresponding STATs to form docking site with the receptor complex and bind to the receptor through its SH2 domain [42]. In response to JAK kinase, STATs are activated by phosphorylation and then form homo/heterodimers for incorporation into the nucleus. Dimeric STATs can bind to the promoters of target genes, and then the transcription of related genes can be activated [43].

During OS, ROS can inactivate tyrosine phosphatases and STAT phosphorylation. STAT3 also up-regulates glutathione to scavenge ROS (**Figure 1**) [44, 45].

Molecular mechanism of OS in sepsis-associated liver injury and antioxidant therapy

Hepatocytes

The roles of ROS production and accumulation in hepatocyte membrane and OS in sepsis-associated liver injury should not be underestimated. The main site of OS damage is the hepatocyte membrane. ROS can degrade unsaturated fatty acids on the hepatocyte membrane into lipid peroxides, which can aggravate the damage to mitochondria [46]. After mitochondria are damaged by ROS, they release cytochrome C into the cytoplasm and cause hepatocyte apoptosis. When sepsis occurs, the content of inducible nitric oxide synthase in the liver is significantly increased. Inducible nitric

Table 1. Signaling pathways and therapeutics of different cellular antioxidant therapies in liver

Types	Signaling pathway	Therapeutic agents
Hepatocyte	mTOR / p70S6K	Albiflorin [53], Anemoside B4 [54]
	Nrf2 / NF-κB	Wogonin [52]
	SIRT1 / STAT3	Melatonin [55]
	SIRT1 / AMPK	Ginsenoside R3 [51]
	Nrf2 / NLRP3	Malvidin [50]
	RAGE / p38	Idebenone [49]
Hepatic stellate cells	VEGF	Dihydroartemisinin [62]
	Nrf-2	Schisandrin B [60]
	ZEB-2 / PTEN	Orientin [59]
	CYP2E/Nrf2 / ROS and PI3K / AKT	Sophocarpine [63]
	ROS / NF-κB	Chlorogenic acid [64]
Hepatic sinusoidal endothelial cells	TLR4 / NFκB	Liquiritigenin and liquiritin [68]
	ROS / ERK	Curcumol [67]
Kupffer cells	CUL3	Pyrroloquinoline quinone [71]
	AMPK	Isoquercetin [72]
	TLR4 / NF-κB / NLRP3	Ginsenoside Rb1 [73]

Note: Nrf2, Nuclear erythrocytes 2-related factor; p70S6K, ribosomal protein S6 kinase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; SIRT1, silent information regulator 1; STAT; signal transducer and activator of transcription; AMPK, adenosine 5'-monophosphate-activated protein kinase; NLRP3, Nucleotide-binding oligomerization domain-like receptor protein 3; RAGE, receptor for advanced glycation end products; VEGF, vascular endothelial growth factor; ZEB-2, zinc finger E-box binding homeobox2; PTEN, phosphatase and tensin homolog; CYP2E1, cytochrome P450 family 2 subfamily E member 1; ROS, reactive oxygen species; ERK, extracellular signal-regulated kinase; PI3K, Phosphatidylinositol 3-kinase; AKT, activate protein kinase B; TLR4, toll-like receptor 4; Cul3, Cullin3.

oxide synthase can induce a large amount of NO, which in turn can react with mitochondrial cytochrome oxidase to inhibit the activity of cytochrome oxidase, and then bring about structural and functional damage on mitochondrial proteins. NO can also react with O^{2-} to generate strong oxidative nitrite peroxide ions, which can oxidize with various molecules, giving rise to apoptosis [47].

Celep et al. found that silymarin could alleviate sepsis-associated liver injury by reducing OS [48]. Gou et al. revealed that Idebenone could prevent sepsis-induced OS, apoptosis, and inflammation by inhibiting RAGE/p38 signaling [49]. Fan et al. discovered that Malvidin prevented the lipopolysaccharide (LPS)-induced decrease in antioxidant enzyme activity by upregulating the Nrf2 pathway, and at the same time inhibited the NLRP3 inflammasome, apoptosis, and autophagy, thereby alleviating sepsis-associated liver injury [50]. Wu et al. reported that ginsenoside Rg3 decreased ROS and stimulated the SIRT1/AMPK pathway, thereby enhancing autophagy to ameliorate sepsis-associated liver injury and mitochondrial dysfunction [51]. Dai et al. demonstrated that Wogonin improved both OS and inflammatory response by activating Nrf2, thus acting as a protective agent against sepsis-associated liver injury [52]. Liu et al. and Pei et al. found that both albiflorin and anemoside B4 inhibited LPS-induced apoptosis and OS of primary hepatocytes through the mTOR/p70S6K signaling pathway, and alleviated liver damage induced by sepsis [53, 54]. Chen et al. and Kleber et al. concluded that melatonin played a protective role in sepsis-induced liver injury by reducing ROS and activating SIRT1/STAT3 pathway [55, 56] (**Table 1**).

Hepatic stellate cells (HSCs)

HSCs are endothelial pericytes located in the hepatic sinusoid space. During liver injury, HSCs are activated into myofibroblasts and secrete extracellular matrix to participate in injury repair. At the same time, the activation of HSCs is also the central link in the development and progression of liver fibrosis [57]. HSCs also bring forth a large number of cytokines, chemokines, and growth mediators and express cell adhesion molecules in response to stimuli such as endotoxin (LPS). Hepatocyte injury results in the release of damage associated molecular patterns, which stimulates HSCs and Kupffer cells (KCs). Further, stimulation of HSCs and KCs recruit immune cells and secrete proinflammatory mediators. Interaction between HSCs and KCs produces a two-way environmen-

tal interaction, leading to the release of pro-inflammatory and anti-inflammatory cytokines. This continued release contributes to ongoing liver damage [58].

It has been found that orientin inhibited HSC activation and reduced LPS and CCl_4-induced liver injury by down-regulating ZEB-2/PTEN [59]. Yao et al. found that schisandrin B attenuated OS in LPS-induced HSC activation through the Nrf2 signaling pathway [60]. Rani et al. revealed that HSCs-sufficient mice treated with acetaminophen exhibited stronger OS compared to HSCs-depleted mice, suggesting that HSCs plays a major role in OS in hepatocytes [61]. Huan et al. found that dihydroartemisinin inhibited HSCs activation by regulating miR-29b-3p to affect vascular endothelial growth factor pathway [62]. Jiang et al. reported that sophocarpine alleviated LPS-induced liver injury, OS and inflammation by inhibiting CYP2E/Nrf2/ROS and PI3K/AKT pathways [63]. Shi et al. demonstrated that chlorogenic acid inhibited LPS-induced proinflammatory responses to HSCS through inhibition of the ROS/NF-κB signaling pathway (**Table 1**) [64].

Hepatic sinusoidal endothelial cells

Liver sinusoidal endothelial cells (LSECs) are highly sensitive to OS. ROS and reactive nitrogen species can reduce the activity of endothelial nitric oxide synthase messenger RNA, leading to dysfunction of LSECs. This dysfunction promotes vasoconstriction, increases intercellular block, raises vascular permeability, and accelerates thrombosis, and further aggravates liver injury [65].

Research indicated that artesunate enhanced the defense of LSECs and prevented the aggregation of inflammatory immune cells, mitigating the effects of sepsis-associated liver injury, inflammation, and dysfunction [66]. Gao et al. demonstrated that curcumin inhibited the angiogenesis of recombinant Kruppel like factor 5-mediated LSECs by inhibiting ROS/ERK signaling [67]. Chen et al. found that glycyrrhizin attenuated cyclophosphamide-induced LSEC injury and inflammatory injury in mice by reducing liver peroxidase activity (**Table 1**) [68]. Pioglitazone can suppress the activation of NF-κB, activator protein-1, MAPK and other inflammatory signaling pathways, and inhibit the release of ROS by KCs, the generation of cytokines and pro-inflammatory mediators, and the expression of adhesion molecule genes in LSECs. Tai et al. discovered that celecoxib reduced ROS through both cyclooxygenase-2 dependent and independent signaling pathways. This reduction in ROS is associated with a significant decrease in NO clearance, subsequently reducing LSEC capillaries and correcting endothelial dysfunction [69].

KCs

KCs are the most important resident macrophages in the liver with abilities of self-renewal, clearance of endotoxin by phagocytosis and release of inflammatory factors to maintain immune homeostasis in the liver. At the same time, during sepsis, KCs can facilitate the development of OS by releasing ROS. KCs further interact with hepatocytes to produce and release chemokines to recruit monocytes in the circulation and subsequently differentiate into monocyte-derived macrophages [70].

Wu et al. found that pyrroloquinoline quinone could inhibit Cul3 expression to alleviate OS and inflammation caused by KCs in sepsis-associated liver injury [71]. Qin et al. revealed that Isoquercetin alleviated inflammation and OS by activating AMPK pathway and inhibiting transforming growth factor β signaling [72]. Liu et al. found that ginsenoside Rb1 attenuated OS and inflammation through TLR4/NF-κB signaling pathway and NLRP3 inflammasome activation [73]. Zhou et al. demonstrated that ultralow doses of dextromethorphan reduced superoxide radicals and alleviated OS in KCs (**Table 1**) [74]. Zhai et al. reported that NADPH oxidase 4 activated the NLRP3 inflammasome through the generation of ROS. This activation promotes the inflammatory response of KC and the release of inflammatory factors, and inhibition of NADPH oxidase 4 ameliorated acute liver injury in mice [75]. Zhang et al. observed that stimulator of interferon genes signaling in KCs enhanced ROS production in response to LPS stimulation, which upgraded mitochondrial DNA release and hepatocyte death, contributing to LPS-induced liver injury [76].

Conclusion

In summary, OS plays an important role in the development and progression of sepsis-associated liver injury. Nrf2, NF-κB, PI3K, NLRP3, MAPK, STAT and other signaling pathways can regulate OS. This review provides the theoretical basis for the antioxidant therapy of sepsis-associated liver injury. Furthermore, liver circulatory and metabolic disorders, excessive inflammatory response, mitochondrial dysfunction, neutrophil and neutrophil extracellular trapping, and autophagy are all mechanisms leading to sepsis associated liver injury. At present, there are many studies on hepatic paren-

chymal cells and KCs in sepsis-associated liver injury. Most of the studies on hepatic stellate cells and hepatic sinusoidal endothelial cells are related to the treatment of liver fibrosis and cirrhosis, but few on sepsis-associated liver injury. This paper summarizes the OS status of different hepatocytes and the treatment of parenchymal and non-parenchymal cells, which can provide ideas for basic clinical research on sepsis related liver injury, so as to reduce the mortality of sepsis related liver injury.

References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama 2016;315:801-810.

[2] Zhu B. Recent advances in the research of viral sepsis. Zhonghua Er Ke Za Zhi 2021;59:250-253.

[3] Zhao GM, Hu ZS. Research progress on the pathogenesis and treatment of sepsis-induced liver injury. Jiefangjun Yixue Zazhi 2019;44:515-520.

[4] Sakr Y, Dubois MJ, De Backer D, et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 2004;32:1825-1831.

[5] Mainali R, Zabalawi M, Long D, et al. Dichloroacetate reverses sepsis-induced hepatic metabolic dysfunction. Elife 2021;10:e64611.

[6] Sakaguchi S, Furusawa S. Oxidative stress and septic shock: metabolic aspects of oxygen-derived free radicals generated in the liver during endotoxemia. FEMS Immunol Med Microbiol 2006;47:167-177.

[7] Xu F, Xu J, Xiong X, et al. Salidroside inhibits MAPK, NF-κB, and STAT3 pathways in psoriasis-associated oxidative stress via SIRT1 activation. Redox Rep 2019;24:70-74.

[8] Diesen DL, Kuo PC. Nitric oxide and redox regulation in the liver: part II. Redox biology in pathologic hepatocytes and implications for intervention. J Surg Res 2011;167:96-112.

[9] Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev 2017;2017:8416763.

[10] Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev 2014;2014:360438.

[11] Lu JQ, Liu JY, Li A. Roles of neutrophil reactive oxygen species (ROS) generation in organ function impairment in sepsis. J Zhejiang Univ-Sci B (Biomed & Biotechnol) 2022;23:437-451.

[12] Borutaite V, Morkuniene R, Arandarcikaite O, et al. Nitric oxide protects the heart from ischemia-induced apoptosis and mitochondrial damage via protein kinase G mediated blockage of permeability transition and cytochrome c release. J Biomed Sci 2009;16:1-12.

[13] Moris D, Spartalis M, Tzatzaki E, et al. The role of reactive oxygen species in myocardial redox signaling and regulation. Ann Transl Med 2017;5:324.

[14] Zhang Z, Rong L, Li YP. Flaviviridae viruses and oxidative stress: implications for viral pathogenesis. Oxid Med Cell Longev 2019;2019:1-17.

[15] Itoh K, Wakabayashi N, Katoh Y, et al. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Genes Dev 1999;13:76-86.

[16] Zhang DD, Lo S, Cross J, et al. Keap1 Is a Redox-Regulated Substrate Adaptor Protein for a Cul3-Dependent Ubiquitin Ligase Complex. Mol Cell Biol 2004;24:10941-10953.

[17] Sajadimajd S, Khazaei M. Oxidative stress and cancer: the role of Nrf2. Curr Cancer Drug Targets 2018;18:538-557.

[18] Otsuki A, Yamamoto M. Cis-element architecture of Nrf2-sMaf heterodimer binding sites and its relation to diseases. Arch Pharm Res 2020;43:275-285.

[19] Mann GE, Niehueser-Saran J, Watson A, et al. Nrf2/ARE regulated antioxidant gene expression in endothelial and smooth muscle cells in oxidative stress: implications for atherosclerosis and preeclampsia. Acta Physiol Sin 2007;59:117-127.

[20] Lee J-M, Johnson JA. An important role of Nrf2-ARE pathway in the cellular defense mechanism. J Biochem Mol Biol 2004;37:139-143.

[21] Zhang J, Wang X, Vikash V, et al. ROS and ROS-mediated cellular signaling. Oxid Med Cell Longev 2016;2016:4350965.

[22] Morgan MJ, Liu ZG. Crosstalk of reactive oxygen species and NF-kappaB signaling. Cell Res 2011;21:103-115.

[23] Ito CY, Kazantsev AG, Baldwin AS. Three NF-kappa B sites in the I kappa B-alpha promoter are required for induction of gene expression by TNF alpha. Nucleic Acids Res 1994;22:3787-3792.

[24] Beinke S, Ley SC. Functions of NF-κB1 and NF-κB2 in immune cell biology. Biochem J 2004;382:393-409.

[25] Xiao G, Harhaj EW, Sun SC. NF-κB-inducing kinase regulates the processing of NF-κB2 p100. Mol Cell 2001;7:401-409.

[26] Sun SC. The non-canonical NF-κB pathway in

immunity and inflammation. Nat Rev Immunol 2017;17:545-558.
[27] Tilstra JS, Gaddy DF, Zhao J, et al. Pharmacologic IKK/NF-kappa B inhibition causes antigen presenting cells to undergo TNF alpha dependent ROS-mediated programmed cell death. Sci Rep 2014;4:3631.
[28] Cross J, Templeton D. Oxidative stress inhibits MEKK1 by site-specific glutathionylation in the ATP-binding domain. Biochem J 2004;381:675-683.
[29] Janssen-Heininger YM, Macara I, Mossman BT. Cooperativity between oxidants and tumor necrosis factor in the activation of nuclear factor (NF)-κ b: requirement of ras/mitogen-activated protein kinases in the activation of Nf-κ B by oxidants. Am J Respir Cell Mol Biol 1999;20:942-952.
[30] Zhang ZX, Heng YQ, Cheng W, et al. Reactive oxygen species (ROS)-response nanomedicine through knocking down a novel therapeutic target NEDD8-conjugating enzyme UBC12 (UBE2M) in the treatment of liver cancer. Mater Des 2021;204:14.
[31] Zhong X, Zhang Z, Shen H, et al. Hepatic NF-κB-Inducing Kinase and Inhibitor of NF-κB Kinase Subunit α Promote Liver Oxidative Stress, Ferroptosis, and Liver Injury. Hepatol Commun 2021;5:1704-1720.
[32] Zhou RB, Tardivel A, Thorens B, et al. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol 2010;11:136-140.
[33] Cui X, Qian DW, Jiang S, et al. Scutellariae Radix and Coptidis Rhizoma Improve Glucose and Lipid Metabolism in T2DM Rats via Regulation of the Metabolic Profiling and MAPK/PI3K/Akt Signaling Pathway. Int J Mol Sci. 2018;19(11):3634.
[34] Morigasaki S, Ikner A, Tatebe H, et al. Response regulator-mediated MAPKKK heteromer promotes stress signaling to the Spc1 MAPK in fission yeast. Mol Biol Cell 2013;24:1083-1092.
[35] Franklin RA, Tordai A, Patel H, et al. Ligation of the T cell receptor complex results in activation of the Ras/Raf-1/MEK/MAPK cascade in human T lymphocytes. J Clin Invest 1994;93:2134-2140.
[36] Williams NG, Paradis H, Agarwal S, et al. Raf-1 and p21v-ras cooperate in the activation of mitogen-activated protein kinase. Proc Natl Acad Sci USA 1993;90:5772-5776.
[37] Tobiume K, Matsuzawa A, Takahashi T, et al. ASK1 is required for sustained activations of JNK/p38 MAP kinases and apoptosis. EMBO Rep 2001;2:222-228.
[38] Haidurov A, Budanov AV. Sestrin family–the stem controlling healthy ageing. Mech Ageing Dev 2020;192:111379.
[39] Kim H, An S, Ro SH, et al. Janus-faced Sestrin2 controls ROS and mTOR signalling through two separate functional domains. Nat Commun 2015;6:10025.
[40] Park SJ, Cho SS, Kim KM, et al. Protective effect of sestrin2 against iron overload and ferroptosis-induced liver injury. Toxicol Appl Pharmacol 2019;379:114665.
[41] Lutticken C, Wegenka UM, Yuan J, et al. Association of transcription factor APRF and protein kinase Jak1 with the interleukin-6 signal transducer gp130. Science 1994;263:89-92.
[42] Schaper F, Gendo C, Eck M, et al. Activation of the protein tyrosine phosphatase SHP2 via the interleukin-6 signal transducing receptor protein gp130 requires tyrosine kinase Jak1 and limits acute-phase protein expression. Biochem J 1998;335:557-565.
[43] Williamson L, Ayalon I, Shen H, et al. Hepatic STAT3 inhibition amplifies the inflammatory response in obese mice during sepsis. Am J Physiol Endocrinol Metab 2019;316:E286-E292.
[44] Linher-Melville K, Singh G. The complex roles of STAT3 and STAT5 in maintaining redox balance: Lessons from STAT-mediated xCT expression in cancer cells. Mol Cell Endocrinol 2017;451:40-52.
[45] Zhang W, Gong M, Zhang W, et al. Thiostrepton induces ferroptosis in pancreatic cancer cells through STAT3/GPX4 signalling. Cell Death Dis 2022;13:630.
[46] Schenk B, Fulda S. Reactive oxygen species regulate Smac mimetic/TNFα-induced necroptotic signaling and cell death. Oncogene 2015;34:5796-5806.
[47] Campolo N, Bartesaghi S, Radi R. Metal-catalyzed protein tyrosine nitration in biological systems. Redox Rep 2014;19:221-231.
[48] Celep NA, Gedikli S. Protective Effect of Silymarin on Liver in Experimental in the Sepsis Model of Rats. Acta Histochem Cytochem 2023;56:9-19.
[49] Gou T, Jin X, Xia J. Idebenone reduces sepsis-induced oxidative stress and apoptosis in hepatocytes via RAGE/p38 signaling. Ann Transl Med 2022;10:1363.
[50] Fan H, Cui J, Liu F, et al. Malvidin protects against lipopolysaccharide-induced acute liver injury in mice via regulating Nrf2 and NLRP3 pathways and suppressing apoptosis and autophagy. Eur J Pharmacol 2022;933:175252.
[51] Wu P, Yu X, Peng Y, et al. Ginsenoside Rg3 alleviates septic liver injury by regulating the lncRNA TUG1/miR-200c-3p/SIRT1 axis. J Inflamm (Lond) 2021;18:31.

[52] Dai JM, Guo WN, Tan YZ, et al. Wogonin alleviates liver injury in sepsis through Nrf2-mediated NF-kappa B signalling suppression. J Cell Mol Med 2021;25:5782-5798.
[53] Liu Y, Feng L, Yao L. Albiflorin alleviates sepsis-induced acute liver injury through mTOR/p70S6K pathway. Curr Mol Med 2023.
[54] Pei L, He L. Hepatoprotective effect of anemoside B4 against sepsis-induced acute liver injury through modulating the mTOR/p70S6K-mediated autophagy. Chem Biol Interact 2021;345:109534.
[55] Chen J, Xia H, Zhang L, et al. Protective effects of melatonin on sepsis-induced liver injury and dysregulation of gluconeogenesis in rats through activating SIRT1/STAT3 pathway. Biomed Pharmacother 2019;117:109150.
[56] Kleber A, Kubulus D, Rössler D, et al. Melatonin modifies cellular stress in the liver of septic mice by reducing reactive oxygen species and increasing the unfolded protein response. Exp Mol Pathol 2014;97:565-571.
[57] Tsuchida T. Mechanisms of hepatic stellate cell activation as a therapeutic target for the treatment of non-alcoholic steatohepatitis. Nihon Yakurigaku Zasshi 2019;154:203-209.
[58] Mooli RGR, Mukhi D, Ramakrishnan SK. Oxidative stress and redox signaling in the pathophysiology of liver diseases. Compr Physiol 2022;12:3167-3192.
[59] Khalil HE, Ibrahim H-IM, El-Fass KA, et al. Orientin Alleviates Liver Inflammation via Downregulation of ZEB-2/PTEN Markers-Hepatic Stellate Cells Approach. Appl Sci -Basel 2022;12:2725.
[60] Yao Z, Han J, Lou S, et al. Schisandrin B attenuates lipopolysaccharide-induced activation of hepatic stellate cells through Nrf-2-activating anti-oxidative activity. Int J Clin Exp Pathol 2018;11:4917-4925.
[61] Rani R, Sharma A, Wang J, et al. Endotoxin-stimulated hepatic stellate cells augment acetaminophen-induced hepatocyte injury. Am J Pathol 2022;192:518-535.
[62] Huan S, Sun S, Song S, et al. Dihydroartemisinin inhibits the activation and proliferation of hepatic stellate cells by regulating miR-29b-3p. Int J Mol Med 2023;51:1-16.
[63] Jiang Z, Meng Y, Bo L, et al. Sophocarpine Attenuates LPS-Induced Liver Injury and Improves Survival of Mice through Suppressing Oxidative Stress, Inflammation, and Apoptosis. Mediators Inflamm 2018;2018:1-12.
[64] Shi H, Dong L, Dang X, et al. Effect of chlorogenic acid on LPS-induced proinflammatory signaling in hepatic stellate cells. Inflamm Res 2013;62:581-587.
[65] Lafoz E, Ruart M, Anton A, et al. The Endothelium as a Driver of Liver Fibrosis and Regeneration. Cells 2020;9:929.
[66] He XL, Chen JY, Feng YL, et al. Single-cell RNA sequencing deciphers the mechanism of sepsis-induced liver injury and the therapeutic effects of artesunate. Acta Pharmacol Sin 2023;44:1801-1814.
[67] Gao L, Yang X, Li Y, et al. Curcumol inhibits KLF5-dependent angiogenesis by blocking the ROS/ERK signaling in liver sinusoidal endothelial cells. Life Sci 2021;264:118696.
[68] Chen M, Zhang C, Zhang J, et al. The involvement of DAMPs-mediated inflammation in cyclophosphamide-induced liver injury and the protection of liquiritigenin and liquiritin. Eur J Pharmacol 2019;856:172421.
[69] Tai Y, Zhao C, Zhang L, et al. Celecoxib reduces hepatic vascular resistance in portal hypertension by amelioration of endothelial oxidative stress. J Cell Mol Med 2021;25:10389-10402.
[70] Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 1989;320:365-376.
[71] Wu Y, Zhao M, Lin Z. Pyrroloquinoline quinone (PQQ) alleviated sepsis-induced acute liver injury, inflammation, oxidative stress and cell apoptosis by downregulating CUL3 expression. Bioengineered 2021;12:2459-2468.
[72] Qin G, Ma J, Huang Q, et al. Isoquercetin Improves Hepatic Lipid Accumulation by Activating AMPK Pathway and Suppressing TGF-beta Signaling on an HFD-Induced Nonalcoholic Fatty Liver Disease Rat Model. Int J Mol Sci 2018;19:4126.
[73] Liu Y, Liu N, Liu Y, et al. Ginsenoside Rb1 Reduces D-GalN/LPS-induced Acute Liver Injury by Regulating TLR4/NF-kappa B Signaling and NLRP3 Inflammasome. J Clin Transl Hepatol 2022;10:474-485.
[74] Zhou R, Chen SH, Li G, et al. Ultralow doses of dextromethorphan protect mice from endotoxin-induced sepsis-like hepatotoxicity. Chem Biol Interact 2019;303:50-56.
[75] Zhai L, Pei H, Yang Y, et al. NOX4 promotes Kupffer cell inflammatory response via ROS-NLRP3 to aggravate liver inflammatory injury in acute liver injury. Aging (Albany NY) 2022;14:6905-6916..
[76] Zhang Q, Wei J, Liu Z, et al. STING signaling sensing of DRP1-dependent mtDNA release in kupffer cells contributes to lipopolysaccharide-induced liver injury in mice. Redox Biol 2022;54:102367.

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Role of intravenous iron therapy for management of perioperative anaemia: A narrative review

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Highlights

- Iron deficiency is the commonest cause for anaemia in patients undergoing surgeries, and this review summarizes its implications.
- Intravenous iron is a better treatment option for iron deficiency than other iron preparations.
- Body iron metabolism is a complex process, and evidence is conflicting on iron supplementation in surgical patients.
- Intravenous iron replacement, as a part of patient blood management, has shown benefit in perioperative anaemia.

Abstract

Anaemia is a frequent problem in surgical patients, and the commonest cause is iron deficiency. There is no agreement among perioperative clinicians on the utility of intravenous (IV) iron therapy in surgical patients. In this study, publications in Medline, Web of Science, and Embase databases, along with major perioperative guidelines up until 2022 were searched using specific key words, and relevant papers that investigated IV iron therapy in the perioperative settings were screened out. Management of perioperative anaemia is comprehensively discussed in major guidelines. However, the diagnosis and management of iron deficiency is not as straightforward as those for anaemia. Iron metabolism is a complex process. IV iron supplementation remains the treatment choice for perioperative iron deficiency; however, it has limited and conflicting evidence of benefits in surgical patients. IV iron replacement, as a part of patient blood management, has shown benefit in perioperative anaemia.

Keywords: Iron, anaemia, perioperative care, surgery, intravenous

Introduction

Anaemia is a common pathological condition, and its prevalence varies from 30% to 75% across patients undergoing elective surgical interventions [1]. Perioperative anaemia is reported in 54.4% patients prior to cardiac surgeries and in 39% undergoing non cardiac surgeries [2].

Anaemia is defined as reduction of body red cell mass, and the World Health Organization criteria for the diagnosis of anaemia are haemoglobin (Hb) level <12 g/dl for women and Hb level <13 g/dl for men [3]. However, the pathological consequences of anaemia in males and females are equivalent during operative procedures, so the lower Hb threshold in females is debatable. Patients undergoing major surgeries with expected blood loss greater than 500 ml should achieve target Hb level >13 g/dl [4]. Cell oxygenation and optimal cellular metabolism require an adequate level of Hb [5, 6]. Anaemia is associated with poor outcomes perioperatively, including intensive care admission, transfusion requirements, extensive length of stay, and mortality [7, 8]. Anaemia in older patients is associated with further increased risk of perioperative complications [9, 10].

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Table 1. Major guidelines on perioperative anaemia and blood management

Guideline	Recommendation on Perioperative anaemia	Class of recommendation	Level of evidence
National Association of Testing Authorities guidelines 2011 [4].	Elective surgical patients should have an Hb level determination as close to 28 days before the scheduled surgical procedure as possible.	1	C
	Patient's target Hb before elective surgery should be within the normal range (female ≥12 g dl^{-1}, male ≥13 g dl^{-1}), according to the World Health Organization criteria.	2	C
European Society of Anaesthesiology guidelines 2016 [12].	Patients at risk of bleeding should be assessed for anaemia 3 to 8 weeks before surgery.	1	C
American Society of Anesthesiologists Task Force on Perioperative Blood Management 2015 [13].	Preoperative evaluation of a patient to identify risk factors for requiring a blood transfusion or adjuvant therapy includes (1) reviewing previous medical records, (2) conducting a patient or family interview, (3) reviewing existing laboratory test results, and (4) ordering additional laboratory tests when indicated.	3/4	B
Patient Blood Management Australia, module 2 Perioperative. March 2012 [14].	Recommendations for multidisciplinary approach in patient blood management during perioperative period.	1/3/4	C

However, the significance of anaemia and its impact on adverse surgical outcomes are undervalued [11]. Routine preoperative investigations should include measuring blood Hb levels, so that treatments could be initiated timely. **Table 1** summarizes the leading available guidelines for perioperative anaemia investigations [4, 12-14].

Iron deficiency (ID) anaemia

Amongst the causes of anaemia, ID is the leading aetiology across all ages, and it is the commonest nutritional deficiency globally [15]. World Health Organization estimates that ID accounts for approximately 50% of all anaemias [16]. Females in childbearing age are more frequently affected by ID than males. It is a problem in both developed and developing countries [17, 18].

Pathophysiology of ID could be absolute or functional. Low or absent iron stores is defined as absolute ID (in contrast to diminished erythropoiesis). High or normal level of iron stores indicate relative or functional ID [15, 19]. Iron metabolism in human body is a complex process which accounts for the above-mentioned types of ID.

Iron (Fe) is a main element of red blood cell Hb and muscle cell myoglobin. Iron is also an important component in enzymes, DNA, and mitochondria. Iron is stored in the form of ferritin and haemosiderin in liver, bone marrow, and spleen [15, 20, 21]. Adults require about 25 mg of elemental iron for red cell Hb production and cellular metabolism daily. However, the average daily intake of iron is only 1 to 2 mg. Due to the limited iron intake, iron homeostasis is maintained by recycling body iron. Older red blood cells are phagocytosed by macrophages, and iron molecules are taken up as a part of the salvage process. Hepcidin is a small peptide secreted mainly from hepatocytes and is the primary regulator of iron homeostasis. Higher iron concentrations and inflammation up-regulate hepcidin production. Hepcidin binds to the ferroprotein, an iron transporting molecule on cell surfaces, and down-regulates its availability. As a result, iron is no longer released to the plasma. This process leads to functional ID in the context of inflammation [19]. Common causes of ID are summarized in **Table 2** [15, 22, 23].

Diagnosis of ID is not as simple as recognition of an apparent ID anaemia. Red cell indices such as mean cell volume and haematocrit are useful markers for assessment of ID. Low mean cell volume corresponds to microcytosis, and low haematocrit is indicative of hypochromia. Presence of these changes in a blood picture suggests long standing ID. Haemoglobinopathies and nutritional deficiencies could alter interpretation of these results [24, 25]. Nevertheless, an iron study is the most useful test to identify ID (See **Table 3**). The ratio of serum iron to total iron binding capacity is presented as transferrin saturation, and a low transferrin saturation usually indicates ID. Serum ferritin levels reflect total body iron stores, and low ferritin is thus indicative of ID. However, acute and chronic inflammatory conditions can elevate ferritin level as a part of the inflammatory process. Low transferrin saturation in the pres-

Table 2. Common causes of iron deficiency

Causes of iron deficiency		
Absolute iron deficiency	Blood loss	Gastro-intestinal bleed, menstrual loss, worm infestation, regular blood donation, other surgery / trauma
	Lack of iron in diet	Vegans, lack of iron rich food
	Malabsorption	Coeliac / Crohn's disease, H. pylori infection, by-pass surgery / small intestinal resection/ gastrectomy, H2 antagonists / proton pump inhibitors
	Increase demand	Infancy and childhood growth, erythropoiesis stimulation treatment, pregnancy
Functional iron deficiency	Anaemia of chronic disease	Heart failure, obesity, cancer, inflammatory diseases, perioperative response

Table 3. Iron study interpretation

Iron study	Level	Diagnosis
Ferritin	<30 mcg/L	Iron deficiency
Ferritin Transferrin saturation	<100 mcg/L <20% (C-reactive protein >5 mg/L)	Iron deficiency + Anaemia with chronic inflammation
Ferritin Transferrin saturation	>100 mcg/L <20% (C-reactive protein >5 mg/L)	Anaemia with chronic inflammation

ence of elevated ferritin levels is suggestive of anaemia of chronic inflammation [26-28].

Treatment for ID

The first approach to manage ID is to treat the underlying cause (See **Table 2**). This is part of the pre-operative assessment. Oral iron therapy increases haemoglobin and reduces perioperative transfusion requirements [29]. However, dietary therapy and oral iron supplements are less effective, mainly due to low efficacy and intolerance [30]. The next available option to treat ID is parenteral iron therapy. Intramuscular injections are available and effective in improving body iron levels; however, intramuscular iron injections are painful and can cause skin staining [31, 32]. There were reported cases of sarcoma after intramuscular iron treatment, hence it remains a less attractive option [33].

Intravenous (IV) iron therapy

IV iron therapy is a choice for perioperative anaemia. Iron dextran was the first successful IV preparation introduced in 1950s. This is a high molecular weight preparation and associated with significant side effects and high risk of anaphylaxis [34]. There are now many other preparations marketed. **Table 4** summarises available iron preparations with their basic properties [35, 36].

Positive evidence for perioperative use of IV iron therapy

IV iron has many advantages in managing perioperative anaemia. Although initial IV iron preparations were less popular due to high incidence of reactions, newer preparations have improved tolerance [37, 38]. The primary benefit of IV iron therapy is the fast response following a single dose. Therefore, IV iron therapy is currently the best option to manage perioperative ID anaemia.

The severity of anaemia has been shown to have a direct relationship with postoperative complications and mortality [39-41]. Preoperative anaemia is an independent risk factor for receiving postoperative blood transfusions [7, 40]. Allogenic blood transfusion has been shown to be associated with adverse outcomes, such as increased infection rates, cardiac complications, hospital length of stay, and mortality [41-45]. These complications are seen even with a transfusion of one unit of packed red blood cells [46]. At the same time, red cell transfusions are relatively expensive [47, 48]. Comprehensive patient blood management programs that include perioperative iron optimisation protocols have been developed to manage preoperative Hb levels and reduce postoperative anaemia and blood transfusions [49-53]. A Cochrane review on the use of perioperative

Table 4. Intravenous iron preparations

Intravenous iron preparation (Carbohydrate substrate)	Brand name	Half-life (Terminal plasma)	Molecular Wt (kDa)
Iron dextran	INFeD, DexFerrum	27-30 hours	103,000
Iron Carboxymaltose	Ferinject	7-9 hours	150,000
Iron sucrose	Venofer, Ferriecit	5-6 hours	43,300
Iron Isomaltosde	Monofer	20-23 hours	69,000
Ferumoxytol	Feraheme	14 -15 hours	185,000
Iron gluconate	Ferrlecit	1-2 hours	37,500

Table 5. Major guidelines on perioperative iron replacement

Guideline	Recommendation	Level of evidence
Patient Blood Management Australia, module 2 Perioperative. March 2012 [14]. *IV iron is indicated when oral not tolerated or rapid correction is required (surgery in <2 months)	Iron therapy is recommended for cases where there is a risk of perioperative iron deficiency anaemia.	B
	Patients with preoperative anaemia should get iron.	A
	For patient with post-operative anaemia, oral iron is not recommended.	B
American Society of Anesthesiologists Task Force on Perioperative Blood Management 2015 [13].	Use of ESA and iron is indicated in risk of anaemia.	A
European Society of Anaesthesiology guidelines 2016 [12].	Oral iron is for patients with iron deficiency diagnosed 6 to 8 weeks before surgery. IV iron for those cannot not tolerated oral iron or closer to the surgery date.	C

Note: ESA, Erythropoietin Stimulating Agents; IV, intravenous.

iron concluded that administration of preoperative IV or oral iron can accelerate Hb recovery and reduce transfusion requirements [54]. However, IV iron therapy showed many benefits over oral iron therapy in perioperative period. It is the only treatment option for preoperative ID when surgery is imminent within 6-8 weeks [12]. Preoperative IV iron therapy demonstrated improved surgical outcomes such as shorter length of stay and higher Hb concentrations at discharge [55-57]. All major blood management guidelines suggest preoperative iron replacement to improve operative outcomes (See **Table 5**).

IV iron therapy is also a viable treatment choice in cases of ID associated with bowel pathology, such as inflammatory bowel disease or bowel resection with poor oral iron absorption [58]. Oral iron is poorly tolerated in these patients due to production of reactive oxygen compounds, such as superoxides and peroxides, from non-absorbed iron salts. This can precipitate acute flares of bowel inflammation. Furthermore, ongoing inflammation in such conditions may cause functional ID as well [59].

Pregnancy and related surgical procedures are other situations where IV iron therapy demonstrates beneficial effects in optimizing Hb and iron levels. Iron supplements are essential during pregnancy to meet the excess demand. Both oral and IV iron supplements are indicated in pregnancy related anaemia or ID [60]. Most studies demonstrated better outcomes with IV iron replacement after childbirth [61]. Considering transfusion reactions and the cost, IV iron therapy is the preferred choice for acute post childbirth anaemia [62].

Severe ID anaemia is best treated with IV iron therapy in both perioperative and non-operative patients. On most occasions, anaemia is diagnosed in pre-operative investigations. All patients undergoing surgical procedures with significant blood loss require iron studies as a part of their preoperative review. When severe ID anaemia is identified in patients who are awaiting surgical procedures, the only treatment option is IV iron therapy. This was reviewed in multiple studies, and the efficacy and potency of IV iron therapy in severe ID have been reported in the literature [55, 56, 63].

Operative or non-operative management of anaemia in cancer patients is usually treated with erythropoietin stimulating agents. However, many studies reported beneficial effects of

Table 6. Risk factors for adverse events from intravenous iron therapy

Risk factors for adverse reactions	Factors increase severity of reaction
Previous hypersensitivity to Intravenous iron History of other allergies Severe asthma or eczema High iron infusion rate	Male sex Older age 1st trimester pregnancy Excess physical activity Beta blocker/Angiotensin converting enzymes Mastocytosis Systemic inflammatory disease Anxiety or psychological issues

combining erythropoietin stimulating agents with IV iron therapy, which improved response to ESA in these patients [64-66]. In fact, absolute and functional ID can co-exist in cancer patients, and IV iron therapy can promote bioavailability of iron for Hb production [65, 66].

Other cohorts of patients who benefit from IV iron therapy are the those with anaemia secondary to chronic kidney disease (CKD). Chronic inflammation in these patients leads to functional ID, and poor oral intake and gastrointestinal bleeding cause absolute ID. Furthermore, patients undergoing dialysis loss blood in each dialysis circuit, contributing to ID. Patients with CKD are frequently on erythropoietin agents which promotes ID due to increased demand of erythropoiesis [67]. This is the reason for using IV iron with Epo in patients with CKD as recommended in Kidney Disease Improving Global Outcomes guidelines [68]. Patients with CKD who are scheduled to undergo surgical procedures should get their Hb and iron levels optimized prior to any surgical interventions, and IV iron therapy combined with erythropoietin is the best option. Peri-operative correction of Hb and iron demonstrated better surgical outcome in CKD patients [4, 69]. However, the ideal level of Hb concentration to achieve optimal surgical outcomes in patients with CKD is not well defined in the literature [70].

Iron can also be given to patients without ID anaemia. Patients with beliefs that preclude the use of blood products (such as Jehovah's Witnesses) benefit from preoperative IV iron dosing to optimize their red cell mass and minimize need for red cell transfusion [71]. Iron is a cofactor in human enzymes. Patients with heart failure and ID were reported to have improved overall outcomes regarding exercise tolerance and heart failure symptoms after IV iron therapy [72, 73]. Therefore, this is an important aspect of optimizing heart failure management prior to surgical procedures.

Disadvantages of IV iron therapy

Perioperative and non-operative IV iron therapy may cause harm as well, but not frequently. The main disadvantage of IV iron therapy is the risk for adverse drug reactions and allergy. The most reported adverse reactions include dizziness, palpitation, urticaria, itching, flushing, and high blood pressure. These are not common and reported in less than 1% of patients. On the other hand, most of these effects are self-limiting [74, 75]. Severe reactions are rare but could lead to life threatening anaphylaxis. Factors predisposing to adverse reactions to IV iron therapy are summarized in **Table 6** [76, 77]. Patho-physiological basis of those reactions is IgE-mediated immunological response and complement activation related pseudo allergy. These responses are partially secondary to labile free irons in the circulation [77]. Management of these reactions are beyond the scope of this article.

Newer IV iron preparations demonstrate less potential for reactions. Iron dextran has high antigenicity effect [77]. Also, dextran-iron high molecular weight compound releases iron faster, causing more rapid increase in free iron levels (See **Table 4**). A follow-up of side effects after IV iron dextran and IV iron gluconate over 3 years revealed an allergic reaction incidence of 21.5% without a difference between two preparations [78]. But most other studies demonstrated a higher incidence of adverse reactions with old-fashioned IV iron preparations, such as iron dextran compared with newer preparations [79, 80].

Another main disadvantage of IV iron supplementation is the potential risk of precipitating infections. This is a debatable issue, and controversial results are found in literature. Extracellular pathogens utilize free iron for their cellular metabolism. IV iron therapy increases free iron in circulation and promotes pathogen activities. This is demonstrated in some animal studies with worsened pneumonia, shock, lung injury, and mortality observed in IV iron group compared to red blood cell transfusion group [81]. Iron is also recognized

as a growth factor for microbes, and a higher incidence of bacterial infection was reported in patients with haemochromatosis experiencing iron overload [82]. Another hypothesis is that retention of iron in macrophages can impair its function. This will affect cellular immunity and increase risk of microbial growth [83]. Another potential mechanism of increasing infection risk is oxidative stress. Sodium ferric gluconate and iron sucrose are responsible for higher non-transferrin bound iron, which is a marker of oxidative stress compared with iron dextran [84]. Oxidative stress was only noted after iron sucrose compared with iron dextran [85]. However, the significance of non-transferrin bound iron in predicting oxidative stress is controversial. Iron loading also accelerates inflammatory response to lipopolysaccharide and produces more superoxide from mitochondria [86]. On the other hand, clinical evidence of increased incidence of infection following iron infusion is lacking. A study investigating infection rate among patients who received no iron, oral iron, and IV iron revealed no significant increase in infection risk [64].

Iron and risk of cancer progression has been discussed for many years. Iron caries carcinogenic potential in some reports [87]. High free iron levels following IV iron therapy could form hydroxyl radicals, and those reactive molecules facilitate lipid peroxidation and oxidative DNA damage. Eventually, the process could lead to tumour growth and angiogenesis [88]. Increased risk of hepatocellular carcinoma in iron overload conditions, such as hereditary haemochromatosis, is possibly related to cirrhosis at the time of cancer diagnosis. Therefore, the relationship between iron overload and cancer is unclear [89]. At the same time, higher iron stores failed to demonstrate increased cancer risk [90]. It is impossible to conduct randomized prospective trials to prove this for ethics concerns.

Conclusion

Anaemia is a common problem during perioperative period, with ID being its leading cause. Pathogenesis of ID is multifactorial. Iron is the main compound in Hb and a vital element of cell metabolism. Diagnosis of anaemia and ID is part of preoperative assessment due to its adverse effect on surgical outcomes and associated increased need for red cell transfusion. IV iron supplementation is the best available treatment for ID and related anaemia perioperatively. There are multiple benefits of IV iron therapy in treating perioperative anaemia. However, safety concerns related to IV iron therapy may counteract some of its beneficial effects. IV iron therapy, as a part of patient blood management strategy, has shown good evidence of benefit [49]. However, as a therapeutic agent, it failed to demonstrate consistent evidence of benefit in perioperative settings. Large scale randomized studies are required to understand the benefit of IV iron supplementation as a treatment for preoperative anaemia.

References

[1] Shander A, Knight K, Thurer R, et al. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. Am J Med 2004;116 Suppl 7A:58s-69s.

[2] Hans GA, Jones N. Preoperative anaemia. Continuing Education in Anaesthesia Critical Care & Pain 2013;13:71-74.

[3] Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Available at: https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1

[4] Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth 2011;106:13-22.

[5] Ince C, Mik EG. Microcirculatory and mitochondrial hypoxia in sepsis, shock, and resuscitation. J Appl Physiol (1985) 2016;120:226-235.

[6] Shander A, Goodnough LT, Javidroozi M, et al. Iron deficiency anemia--bridging the knowledge and practice gap. Transfus Med Rev 2014;28:156-166.

[7] Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011;378:1396-1407.

[8] Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348:1055-1060.

[9] Bailes BK. Perioperative Care of the Elderly Surgical Patient. AORN J 2000;72:185-207.

[10] Auron M, Castillo MYD. Preoperative anemia optimization: role of iron supplementation. J Xiangya Med 2018;3:37.

[11] Lagoo J, Wilkinson J, Thacker J, et al. Impact of anemia on surgical outcomes: innovative interventions in resource-poor settings. World J Surg 2012;36:2080-2089.

[12] Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol 2017;34:332-395.

[13] American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology 2015;122:241-275.
[14] Patient Blood Management Guidelines: Module 2 Perioperative. Available at: https://blood.gov.au/pbm-module-2
[15] Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. Lancet 2016;387:907-916.
[16] Stoltzfus RJ. Iron deficiency: global prevalence and consequences. Food Nutr Bull 2003;24:S99-S103.
[17] Perez-Escamilla R, Bermudez O, Buccini GS, et al. Nutrition disparities and the global burden of malnutrition. BMJ 2018;361:k2252.
[18] Saad RA, Qutob HM. The relationship between anemia and obesity. Expert Rev Hematol 2022;15:911-926.
[19] Busti F, Campostrini N, Martinelli N, et al. Iron deficiency in the elderly population, revisited in the hepcidin era. Front Pharmacol 2014;5:83.
[20] Finch CA, Hegsted M, Kinney TD, et al. Iron metabolism; the pathophysiology of iron storage. Blood 1950;5:983-1008.
[21] Kohgo Y, Ikuta K, Ohtake T, et al. Body iron metabolism and pathophysiology of iron overload. Int J Hematol 2008;88:7-15.
[22] Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician 2007;75:671-678.
[23] Camaschella C. Iron-deficiency anemia. N Engl J Med 2015;372:1832-1843.
[24] Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med 1992;7:145-153.
[25] Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. Am Fam Physician 2013;87:98-104.
[26] Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol 2005;18:319-332.
[27] Punnonen K, Irjala K, Rajamäki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood 1997;89:1052-1057.
[28] Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017;72:233-247.
[29] Lidder PG, Sanders G, Whitehead E, et al. Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - a prospective, randomised, controlled trial. Ann R Coll Surg Engl 2007;89:418-421.
[30] Petis SM, Lanting BA, Vasarhelyi EM, et al. Is There a Role for Preoperative Iron Supplementation in Patients Preparing for a Total Hip or Total Knee Arthroplasty? J Arthroplasty 2017;32:2688-2693.
[31] Baird IM, Podmore DA. Intramuscular iron therapy in iron-deficiency anaemia. Lancet 1954;267:942-946.
[32] Treatment of iron deficiency anemia in adults. Available at: https://www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults
[33] Grasso P. Sarcoma after intramuscular iron injection. Br Med J 1973;2:667.
[34] Cançado RD, Muñoz M. Intravenous iron therapy: how far have we come? Rev Bras Hematol Hemoter 2011;33:461-469.
[35] Neiser S, Rentsch D, Dippon U, et al. Physico-chemical properties of the new generation IV iron preparations ferumoxytol, iron isomaltoside 1000 and ferric carboxymaltose. Biometals 2015;28:615-635.
[36] Martin-Malo A, Borchard G, Flühmann B, et al. Differences between intravenous iron products: focus on treatment of iron deficiency in chronic heart failure patients. ESC Heart Fail 2019;6:241-253.
[37] Kumpf VJ. Parenteral iron supplementation. Nutr Clin Pract 1996;11:139-146.
[38] Kumpf VJ. Update on parenteral iron therapy. Nutr Clin Pract 2003;18:318-326.
[39] Beattie WS, Karkouti K, Wijeysundera DN, et al. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology 2009;110:574-581.
[40] Baron DM, Hochrieser H, Posch M, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth 2014;113:416-423.
[41] Dunkelgrun M, Hoeks SE, Welten GM, et al. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. Am J Cardiol 2008;101:1196-1200.
[42] Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg 2012;256:235-244.
[43] Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. N Engl J Med 2006;355:1303-1305.
[44] Goodnough LT. Risks of blood transfusion. Anesthesiol Clin North Am 2005;23:241-252.
[45] Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery.

Anesthesiology 2011;114:283-292.
[46] Bernard AC, Davenport DL, Chang PK, et al. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 2009;208:931-937.
[47] Toner RW, Pizzi L, Leas B, et al. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. Appl Health Econ Health Policy 2011;9:29-37.
[48] Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010;50:753-765.
[49] Ferraris VA, Davenport DL, Saha SP, et al. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. Arch Surg 2012;147:49-55.
[50] Kotzé A, Carter LA, Scally AJ. Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: a quality improvement cycle. Br J Anaesth 2012;108:943-952.
[51] Spahn DR, Moch H, Hofmann A, et al. Patient blood management: the pragmatic solution for the problems with blood transfusions. Anesthesiology 2008;109:951-953.
[52] Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion 2017;57:1347-1358.
[53] Meybohm P, Herrmann E, Steinbicker AU, et al. Patient Blood Management is Associated With a Substantial Reduction of Red Blood Cell Utilization and Safe for Patient's Outcome: A Prospective, Multicenter Cohort Study With a Noninferiority Design. Ann Surg 2016;264:203-211.
[54] Gurusamy KS, Nagendran M, Broadhurst JF, et al. Iron therapy in anaemic adults without chronic kidney disease. Cochrane Database Syst Rev 2014;2014:Cd010640.
[55] Peters F, Ellermann I, Steinbicker AU. Intravenous Iron for Treatment of Anemia in the 3 Perisurgical Phases: A Review and Analysis of the Current Literature. Anesth Analg 2018;126:1268-1282.
[56] Wilson MJ, Dekker JW, Bruns E, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. Transfusion 2018;58:795-803.
[57] Heschl M, Gombotz H, Haslinger-Eisterer B, et al. The efficacy of pre-operative preparation with intravenous iron and/or erythropoietin in anaemic patients undergoing orthopaedic surgery: An observational study. Eur J Anaesthesiol 2018;35:289-297.
[58] Muñoz M, Gómez-Ramírez S, García-Erce JA. Intravenous iron in inflammatory bowel disease. World J Gastroenterol 2009;15:4666-4674.
[59] Crichton RR, Danielson BG, Geisser P. Iron therapy with special emphasis on intravenous administration. UNI-MED Verlag. 2008.
[60] Seeho SKM, Morris JM. Intravenous iron use in pregnancy: Ironing out the issues and evidence. Aust N Z J Obstet Gynaecol 2018;58:145-147.
[61] Holm C. Intravenous iron treatment in the puerperium. Dan Med J 2018;65:B5471.
[62] Chua S, Gupta S, Curnow J, et al. Intravenous iron vs blood for acute post-partum anaemia (IIBAPPA): a prospective randomised trial. BMC Pregnancy Childbirth 2017;17:424.
[63] Shin HW, Park JJ, Kim HJ, et al. Efficacy of perioperative intravenous iron therapy for transfusion in orthopedic surgery: A systematic review and meta-analysis. PLoS One 2019;14:e0215427.
[64] Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231-242.
[65] Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611-1618.
[66] Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol 2014;89:203-212.
[67] Zadrazil J, Horak P. Pathophysiology of anemia in chronic kidney diseases: A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015;159:197-202.
[68] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.
[69] Palevsky PM. Perioperative management of patients with chronic kidney disease or ESRD. Best Pract Res Clin Anaesthesiol 2004;18:129-144.
[70] Shavit L, Hitti S, Silberman S, et al. Preoperative hemoglobin and outcomes in patients with CKD undergoing cardiac surgery. Clin J Am Soc Nephrol 2014;9:1536-1544.

[71] Lawson T, Ralph C. Perioperative Jehovah's Witnesses: a review. Br J Anaesth 2015;115:676-687.

[72] Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail 2016;18:786-795.

[73] Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. Eur Heart J 2015;36:657-668.

[74] Chertow GM, Mason PD, Vaage-Nilsen O, et al. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378-382.

[75] Miller HJ, Hu J, Valentine JK, et al. Efficacy and tolerability of intravenous ferric gluconate in the treatment of iron deficiency anemia in patients without kidney disease. Arch Intern Med 2007;167:1327-1328.

[76] Lim W, Afif W, Knowles S, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. Vox Sang 2019;114:363-373.

[77] Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica 2014;99:1671-1676.

[78] Eichbaum Q, Foran S, Dzik S. Is iron gluconate really safer than iron dextran? Blood 2003;101:3756-3757.

[79] Bailie GR, Clark JA, Lane CE, et al. Hypersensitivity reactions and deaths associated with intravenous iron preparations. Nephrol Dial Transplant 2005;20:1443-1449.

[80] Wang C, Graham DJ, Kane RC, et al. Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products. Jama 2015;314:2062-2068.

[81] Suffredini DA, Xu W, Sun J, et al. Parenteral irons versus transfused red blood cells for treatment of anemia during canine experimental bacterial pneumonia. Transfusion 2017;57:2338-2347.

[82] Marx JJ. Iron and infection: competition between host and microbes for a precious element. Best Pract Res Clin Haematol 2002;15:411-426.

[83] Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. Ann Pharmacother 2007;41:1476-1480.

[84] Pai AB, Boyd AV, McQuade CR, et al. Comparison of oxidative stress markers after intravenous administration of iron dextran, sodium ferric gluconate, and iron sucrose in patients undergoing hemodialysis. Pharmacotherapy 2007;27:343-350.

[85] Stefánsson BV, Haraldsson B, Nilsson U. Acute oxidative stress following intravenous iron injection in patients on chronic hemodialysis: a comparison of iron-sucrose and iron-dextran. Nephron Clin Pract 2011;118:c249-c256.

[86] Hoeft K, Bloch DB, Graw JA, et al. Iron Loading Exaggerates the Inflammatory Response to the Toll-like Receptor 4 Ligand Lipopolysaccharide by Altering Mitochondrial Homeostasis. Anesthesiology 2017;127:121-135.

[87] Greenberg G. Sarcoma after intramuscular iron injection. Br Med J 1976;1:1508-1509.

[88] Toyokuni S. Role of iron in carcinogenesis: cancer as a ferrotoxic disease. Cancer Sci 2009;100:9-16.

[89] Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology 2004;127:S79-S86.

[90] Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and meta-analysis of the epidemiological evidence. Cancer Epidemiol Biomark Prev 2014;23:12-31.

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Application of electroencephalography in the management of postoperative cognitive dysfunction

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Highlights

- Maintaining anesthesia depth within specific ranges, as indicated by electroencephalography monitors, may reduce the risk of postoperative cognitive dysfunction.
- Quantitative analysis of electroencephalography data can provide insights into the characteristics of postoperative cognitive dysfunction, aiding in its early detection and diagnosis.
- Combining electroencephalography with functional magnetic resonance imaging may enhance the assessment of brain function and improve the accuracy of monitoring devices.

Abstract

Postoperative cognitive dysfunction (POCD) is a common postoperative complication in elder patients, elevating the risk of dementia, impacting patient prognosis, and adding to the socio-economic burden. Electroencephalography (EEG) enables the recording of brain electrical activity and reflects the state of consciousness. Changes in the electrogram may signal diverse pathological and physiological states. Currently, EEG and its associated monitoring devices are extensively utilized in clinical practice. This paper presents a thorough review of the use of EEG in POCD research, aiming to establish a more substantial foundation for the prediction and prevention of POCD.

Keywords: Electroencephalography, depth of anesthesia, postoperative cognitive dysfunction, postoperative neurocognitive disorder

Introduction

Postoperative cognitive dysfunction (POCD) primarily comprises delayed neurocognitive recovery within 30 days after surgery and postoperative neurocognitive dysfunction up to or beyond 12 months. It is a subset of perioperative neurocognitive disorder, a broader category that includes both cognitive decline before surgery and postoperative delirium [1, 2].

POCD is a long-term and potentially reversible neurological complication that predominantly seen in elderly patients after major surgery. It seriously impairs patients' learning ability and memory, reduces their one-year survival rate after surgery, increases the risk of dementia, and prolongs patients' hospitalization, which inevitably adds to socio-economic burden [1, 3-7]. POCD affects an estimated 12% of patients with previously unimpaired cognitive function undergoing non-cardiac surgery under anesthesia [8]. While POCD is more prevalent in seniors, its incidence is also high among other age groups. With the aging of society, an increasing number of patients will undergo surgical treatment, potentially leading to a rise in the incidence of POCD. Therefore, in recent years, POCD has garnered considerable attention from scholars across various disciplines.

The exact pathogenesis of POCD remains un-

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clear; however, plausible risk factors include cerebral oxygen saturation, neuroinflammation, stress response, temperature changes, genetic predispositions, residual effects of anesthesia drugs, anesthesia drug toxicity, hypoxia, reduced cerebral blood flow perfusion, and central cholinergic dysfunction [6, 9-12]. POCD may also display a link to Alzheimer's disease (AD) through mechanisms such as amyloid β-protein accumulation and neuroinflammation [10, 13, 14]. Previous research has demonstrated the significance of electroencephalography (EEG) indicators in the early diagnosis of AD and vascular cognitive impairment [15]. The quantitative analysis of EEG may be one of the potential methods for identifying biomarkers of cognitive impairment, offering insights into predicting and diagnosing POCD [16]. Exploring whether there is a correlation between perioperative EEG metrics – indicated brain functional state and POCD and whether these indicators can predict POCD is a valuable research topic.

Definition and basic principles of EEG

The electrical signals in brain primarily derived from the synchronous summation of the postsynaptic potentials of a large number of pyramidal neurons in the cerebral cortex, which is the result of collective neuronal activity. German psychiatrist Hans Berger systematically analyzed the electrical activity of the brain and introduced the term "electroencephalogram" to describe the recorded electrical potential fluctuations of the brain.

EEG amplifies and records the brain electrical signals using external scalp electrodes, yielding complex waveforms. In perioperative settings, EEG is commonly used to record spontaneous brain activity, with two most common approaches: raw EEG (rEEG) and processed EEG. rEEG records the brain electrical signals generated by postsynaptic currents within the cortical and subcortical regions of the brain. The frequency range of raw brain electrical signals spans from 0.3 to 45.0 Hz, and rEEG frequencies are subdivided into various groups based on different frequencies: delta waves (0.4-4.0 Hz), theta waves (4-8 Hz), alpha waves (8-13 Hz), beta waves (13-30 Hz), and gamma waves (30-45 Hz) [17]. Waves above alpha waves are termed fast waves, while those below alpha waves are termed slow waves. However, interpretation of complex EEG waveforms can be challenging for non-specialist anesthetists, which has led to the development of processed EEG based on cortical electrical activity, such as bispectral index (BIS) monitors, narcotrend monitors, and entropy index monitors.

Progress of EEG in POCD

Application of processed EEG in POCD research

With the widespread use of EEG monitors in clinical practice, an increasing number of anesthetists can now assess the depth of anesthesia. Research has demonstrated that monitoring the depth of anesthesia, particularly in elderly patients, facilitates quicker recovery from anesthesia and lessens the occurrence of postoperative nausea and vomiting. Currently, there is no definitive academic conclusion on whether the occurrence of POCD can be predicted by the depth of anesthesia [18-23].

BIS

Currently, BIS is the most widely used EEG monitor in clinic. The EEG data are transformed into numbers by BIS, ranging from 0 to 100, to indicate the level of brain activity inhibition. A value of 100 shows that the brain is fully awake and a value of 0 shows that the brain is completely suppressed [24]. Several studies have recommended using BIS to monitor anesthesia depth as it may lower the occurrence of POCD. Ballard et al. demonstrated that monitoring anesthesia depth with BIS during operations could effectively prevent the occurrence of POCD [25]. Similar results were found by Chan et al., where anesthesia guided by BIS reduced the incidence of POCD at 3 months post-operation [26]. Monitoring the anesthesia depth during operation can therefore be seen as a practical measure to reduce the incidence of POCD. Chen et al. asserted the effectiveness of BIS in reducing delayed neurocognitive recovery and postoperative neurocognitive impairment, regardless of patients' age [7]. A systematic review and meta-analysis of EEG on perioperative neurological dysfunction involving 4,976 patients has demonstrated that employing BIS monitoring during surgery is associated with a lower risk of POCD [27].

Whilst numerous scholars have demonstrated that using BIS to monitor depth of anesthesia can reduce the incidence of POCD, there is still no consensus on the optimal BIS range for effectively minimizing the incidence of POCD. For elderly patients undergoing abdominal surgery, Shi et al. proposed that maintaining BIS between 45 and 60 could stabilize perioperative hemodynamics, reduce the risk of early-onset POCD, shorten the awakening time from anesthesia, and improve early postoperative cognitive function [28]. An et al. held that the use of BIS monitoring could avoid deep anesthesia

and thus effectively reduce the incidence of POCD [29]. However, in a study using BIS to monitor the depth of anesthesia, Yue et al. observed that the proportion of patients with abnormal Mini-Mental State Examination score in the deep anesthesia group after surgery was significantly lower than that in the light anesthesia group, suggesting that deep anesthesia causes less cognitive impairment in patients [30]. A meta-analysis by Shi et al. showed that the incidence of early POCD was lower under deep anesthesia (BIS: 30-40) compared to conventional anesthesia [6]. Nevertheless, there is still a lack of comprehensive research, and the available randomized controlled trials do not provide sufficient data to compare the incidence of POCD at postoperative 3 or 7 days. Quan et al. reported that the incidence of POCD at postoperative day 7 was significantly lower in the deep anesthesia group (BIS: 30-45) than in the light anesthesia group (BIS: 45-60) (19.2% vs. 39.6%, p=0.032), but there was no statistical difference in the incidence of POCD between the two groups at 3 months after surgery (10.3% vs. 14.6%, p=0.558) [31]. Compared with light anesthesia, deep anesthesia is associated with a lower incidence of short-term POCD and a reduced release of inflammatory cytokines in elderly patients undergoing abdominal surgery [31]. Hou et al. considered perioperative pain as a potential factor contributing to POCD and thus excluded potential bias caused by inadequate preoperative nerve block analgesia in their study. Their results showed that in elderly patients undergoing total knee replacement surgery, lighter anesthesia (BIS: 55-65) coupled with complete nerve block analgesia reduced the incidence of POCD, whereas patients under deep anesthesia had a higher incidence of POCD [32].

Some research has indicated a possible link between burst suppression in EEG and postoperative delirium [33]. This sheds light on the direction of POCD research. Deiner et al. found that the lengths of burst suppression and deep anesthesia state in POCD patients were shorter, indicating that burst suppression and deep anesthesia may have a protective effect on POCD [34]. Dustin et al. discovered that the POCD patients experienced a significant increase in the duration of burst suppression during surgery [35]. However, it cannot be deduced that burst suppression has a clear causal relationship with POCD. This discovery can assist the application of intraoperative rEEG to study POCD in the future. Some researchers have explored the correlation between BIS values and biochemical markers of POCD, such as serum S100β, which is an acidic protein that binds calcium and impacts glial cell growth and memory function. Serum S100β offers a dependable reflection of brain injury with high specificity [36]. Several studies have suggested that maintaining BIS at 30-39 benefits elderly patients undergoing abdominal surgery by significantly reducing serum S100β level and mitigating brain injury, thereby reducing the incidence of POCD [30]. Other scholars have proposed the concept of 'BIS awake', which is the mean value of BIS when the concentration of disoprofol effector compartment drops to 1 ug/ml after the target-controlled infusion of disoprofol is stopped. Their study found that a BIS awake of <65 postoperatively might be a predictor of some impaired cognitive functions related to word memory [37].

Narcotrend

Narcotrend is a new type of anesthesia monitoring device that uses standard EEG electrodes to acquire and evaluate real-time EEG signals from any part of the patient's head, such as raw EEG or visual EEG. Through automated analysis, it displays the depth of anesthesia or consciousness of patients. This device allows for adjustments in the dosage of anesthetics or sedatives based on the patient's specific condition, thereby enhancing the precision of anesthesia depth and improving safety and convenience [38, 39]. It divides the rEEG into six stages and 15 levels, namely A (wakefulness), B0-B2 (sedation), C0-C2 (light anesthesia), D0-D2 (general anesthesia), E0-E2 (deep anesthesia), and F0-F2 (burst suppression), using a dimensionless anesthesia depth index (Narcotrend index) ranging from 0-100 to reflect the entire process from wakefulness to deep anesthesia [6, 38]. Narcotrend outperforms BIS as it not only distinguishes consciousness states over a broad range but also monitors sudden changes in the depth of anesthesia [40]. In a study conducted by Zeng et al. on the effects of Narcotrend on POCD, they discovered that the occurrence of POCD in patients subjected to deep anesthesia was considerably lower compared to those under light anesthesia [39]. The research highlights the value of utilizing deep anesthesia to minimize the risk of POCD. Chen et al. suggested that maintaining the depth of anesthesia within a Narcotrend index of 30-39 could improve cerebral oxygen metabolism, inhibit inflammatory reactions, and reduce the incidence of POCD in elderly patients undergoing thoracoscopic lobectomy [41]. This monitoring device can accurately reflect the level of anesthesia in each stage and can be widely applied in clinical practice to reduce the occurrence of POCD.

Other EEG monitors

The Sedline EEG monitor offers an advanced analysis of raw EEG waveform and displays the patient's current state index, density spectral array, and spectral edge frequency. Compared to the BIS and Narcotrend monitors, Sedline provides more accurate assessment of the anesthesia depth by eliminating electromyographic interference to a certain extent, and it can also identify the specific type of general anesthetic in use. However, its use for predicting POCD is still inconclusive [42]. The index of consciousness (IoC) is another novel approach to depict anesthesia depth, which quantifies EEG signals into an IoC index. Research has shown that IoC monitoring is more accurate in assessing anesthesia depth compared to BIS, and its application can significantly reduce the occurrence of POCD in colorectal cancer patients [43]. The entropy index monitor collects EEG signals and frontal electromyographic data and converts them into state entropy and reaction entropy values, representing the depth of anesthesia. State entropy and reaction entropy are indicators ranging from 0 to 91 and 0 to 100, respectively, which represent the transition from complete suppression of cortical neuronal activity to wakefulness [44]. Cotae et al. concluded that utilizing entropy index-guided anesthesia in patients undergoing non-cardiac emergency surgery may decrease the occurrence of POCD when compared to standard monitoring [45]. These EEG monitors are less widely used in clinical practice compared to BIS and Narcotrend devices, and there exists limited research on their application in POCD. However, there is currently no evidence indicating the superiority of any specific EEG quantification index in monitoring the depth of anesthesia or predicting patient prognosis. Further studies are required to substantiate the effectiveness of EEG monitors in POCD research.

Application of rEEG and quantitative EEG in POCD studies

Above studies have investigated the effect of anesthesia depth on POCD by quantitative analysis of EEG data. However, there are few experiments investigating the characteristic changes in the rEEG or quantitative EEG of POCD patients.

Prediction of POCD

Some studies have suggested that the reduction of α power in older adults during surgery is related to preoperative cognitive decline, further research is needed to ascertain the link between reduced α power in the frontal lobe and POCD [4]. Nevertheless, they also acknowledged the potential application of EEG in the prevention of POCD, believing that the reduction of α power during surgery may serve as a biomarker to identify patients with possible impaired preoperative cognitive function, allowing for intervention to prevent POCD. In the study by Hao et al., it was pointed out that the γ power ratio after anesthesia was lower than that in the awake state in the non-POCD group, and in the anesthetic state, the percentage of δ power in the total power was significantly higher in the POCD group than in the non-POCD group [46]. There were differences in EEG patterns between POCD and non-POCD patients, but the reduction in α power ratio and α power may not be risk factors for the occurrence of POCD [46]. θ band activity in the EEG is one of the most sensitive indicators of perioperative brain injury, and the increase in θ power in the EEG is associated with mild cognitive impairment and dementia [47, 48]. In a study evaluating the effects of preoperative aerobic physical training (PhT) on neurophysiological function and neurovascular biomarkers in patients undergoing coronary artery bypass grafting, it was found that patients who received PhT before surgery were less likely to suffer from POCD [16]. EEG data showed that patients who received preoperative PhT had a less pronounced increase in slow wave θ activity after surgery, indicating a lower degree of intraoperative brain injury. This provides a new approach to prevent the occurrence of POCD. Another study suggested that high frequency β rhythm power was associated with POCD in patients undergoing coronary artery bypass grafting [17]. The elevated β activity in the right frontal region and the reduced power of high frequency β oscillations in the left parietal region before surgery may serve as predictive factors for cognitive decline. Evaluation of the topographic features and dynamic processes of cortical high-frequency activity patterns may help to develop individualized rehabilitation plans for patients with POCD.

Diagnosis of POCD

In the study by Zhang et al., the characteristics of quantitative EEG in POCD patients were investigated, providing new insights into the study of EEG in POCD [49]. Their study showed that the α band energy and α variability in the EEG of POCD patients were significantly lower than those of the non-POCD control group, and they were significantly correlated with the Mini-Mental State Examination score, suggesting that directional EEG may have clinical significance in the detection and diagnosis of POCD.

Prospects of using Simultaneous EEG-functional MRI (fMRI) in POCD research

fMRI indirectly reflects neural activities by measuring local blood flow metabolism. However, it is constrained by the slow hemodynamic response, with changes in blood flow occurring several seconds after changes in neural activity [50]. By combining with EEG, fMRI identifies activated brain regions and links them to specific neural responses measured by EEG at specific times, providing advantages in both temporal and spatial resolution [51]. The simultaneous EEG-fMRI facilitates the study of various cognitive functions, such as language, memory, emotion, and auditory and visual perception, through a variety of cognitive tasks, making it a leading technique in cognitive research in recent years. Cichy et al. proposed that EEG-fMRI has the potential for effectively revealing the spatiotemporal dynamics of human cognitive function [52]. Its future application in POCD research is promising.

Conclusion

Currently, EEG are commonly used in clinical practice to monitor the depth of anesthesia, although there still lacks definitive consensus on the relationship between anesthesia depth and POCD. The amplitude and frequency of the EEG change with age, which questions the accuracy of using EEG to assess the depth of anesthesia in different age groups. In addition, EEG and its derived indices can be affected by various factors, including electromyographic interference, neuromuscular blocking agents, use of medical devices, pacemakers, and compound anesthesia. It is hoped that monitoring devices can be optimized to reduce the interference of these confounding factors in the future, making intraoperative EEG monitoring more accurate and generating more accurate and consistent conclusions in future research. Furthermore, studies on the alterations in the rEEG of patients with POCD are still few. Whether it is possible to intervene and treat early POCD based on the changes in the EEG characteristics is to be expected.

References

[1] Tang X, Zhang X, Dong H, et al. Electroencephalogram Features of Perioperative Neurocognitive Disorders in Elderly Patients: A Narrative Review of the Clinical Literature. Brain Sci 2022;12:1073.

[2] Evered LA, Goldstein PA. Reducing Perioperative Neurocognitive Disorders (PND) Through Depth of Anesthesia Monitoring: A Critical Review. Int J Gen Med 2021;14:153-162.

[3] Steinmetz J, Christensen KB, Lund T, et al. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110:548-555.

[4] Giattino CM, Gardner JE, Sbahi FM, et al. Intraoperative Frontal Alpha-Band Power Correlates with Preoperative Neurocognitive Function in Older Adults. Front Syst Neurosci 2017;11:24.

[5] Jildenstål PK, Rawal N, Hallén JL, et al. Perioperative management in order to minimise postoperative delirium and postoperative cognitive dysfunction: Results from a Swedish web-based survey. Ann Med Surg (Lond) 2014;3:100-107.

[6] Shi X, Chen X, Ni J, et al. Systematic review and meta-analysis of the prognostic value of Narcotrend monitoring of different depths of anesthesia and different Bispectral Index (BIS) values for cognitive dysfunction after tumor surgery in elderly patients. Ann Transl Med 2022;10:186.

[7] Chen X, Li L, Yang L, et al. A randomized trial: bispectral-guided anesthesia decreases incidence of delayed neurocognitive recovery and postoperative neurocognitive disorder but not postoperative delirium. Am J Transl Res 2022;14:2081-2091.

[8] Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. Br J Anaesth 2017;119:i115-i125.

[9] Berger M, Oyeyemi D, Olurinde MO, et al. The INTUIT Study: Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction. J Am Geriatr Soc 2019;67:794-798.

[10] Hu Z, Ou Y, Duan K, et al. Inflammation: a bridge between postoperative cognitive dysfunction and Alzheimer's disease. Med Hypotheses 2010;74:722-724.

[11] Chawdhary AA, Kulkarni A, Nozari A. Substitution of propofol for dexmedetomidine in the anaesthetic regimen does not ameliorate the post-operative cognitive decline in elderly patients. Indian J Anaesth 2020;64:880-886.

[12] Vacas S, Degos V, Feng X, et al. The neuroinflammatory response of postoperative cognitive decline. Br Med Bull 2013;106:161-178.

[13] Kapila AK, Watts HR, Wang T, et al. The impact of surgery and anesthesia on post-operative cognitive decline and Alzheimer's disease development: biomarkers and preventive strategies. J Alzheimers Dis 2014;41:1-13.

[14] Steinmetz J, Siersma V, Kessing LV, et al. Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study. Br J Anaesth 2013;110 Suppl 1:i92-i97.

[15] Mazzon G, De Dea F, Cattaruzza T, et al.

Memorization Test and Resting State EEG Components in Mild and Subjective Cognitive Impairment. Curr Alzheimer Res 2018; 15:809-819.

[16] Trubnikova OA, Tarasova IV, Moskin EG, et al. Beneficial Effects of a Short Course of Physical Prehabilitation on Neurophysiological Functioning and Neurovascular Biomarkers in Patients Undergoing Coronary Artery Bypass Grafting. Front Aging Neurosci 2021;13: 699259.

[17] Tarasova IV, Razumnikova OA, Trubnikova OA, et al. Neurophysiological correlates of postoperative cognitive disorders. Zh Nevrol Psikhiatr Im S S Korsakova 2021;121:18-23.

[18] Steinmetz J, Funder KS, Dahl BT, et al. Depth of anaesthesia and post-operative cognitive dysfunction. Acta Anaesthesiol Scand 2010; 54:162-168.

[19] Ling L, Yang TX, Lee SWK. Effect of Anaesthesia Depth on Postoperative Delirium and Postoperative Cognitive Dysfunction in High-Risk Patients: A Systematic Review and Meta-Analysis. Cureus 2022;14:e30120.

[20] Li Y, Zhang B. Effects of anesthesia depth on postoperative cognitive function and inflammation: a systematic review and meta-analysis. Minerva Anestesiol 2020;86:965-973.

[21] Zhou Y, Li Y, Wang K. Bispectral Index Monitoring During Anesthesia Promotes Early Postoperative Recovery of Cognitive Function and Reduces Acute Delirium in Elderly Patients with Colon Carcinoma: A Prospective Controlled Study using the Attention Network Test. Med Sci Monit 2018;24:7785-7793.

[22] Bocskai T, Kovács M, Szakács Z, et al. Is the bispectral index monitoring protective against postoperative cognitive decline? A systematic review with meta-analysis. PLoS One 2020;15:e0229018.

[23] Lu X, Jin X, Yang S, et al. The correlation of the depth of anesthesia and postoperative cognitive impairment: A meta-analysis based on randomized controlled trials. J Clin Anesth 2018;45:55-59.

[24] Chiang MH, Wu SC, Hsu SW, et al. Bispectral Index and non-Bispectral Index anesthetic protocols on postoperative recovery outcomes. Minerva Anestesiol 2018;84:216-228.

[25] Ballard C, Jones E, Gauge N, et al. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. PLoS One 2012;7:e37410.

[26] Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013;25:33-42.

[27] Ding L, Chen DX, Li Q. Effects of electroencephalography and regional cerebral oxygen saturation monitoring on perioperative neurocognitive disorders: a systematic review and meta-analysis. BMC Anesthesiol 2020;20: 254.

[28] Shi LD, Zhang ML, Zhu SK, et al. Correlation between bispectral index of depth of anesthesia and postoperative cognitive dysfunction in elderly patients with abdominal surgery. China Mod Doct 2023;61:25-29+46.

[29] An ST, Wang Y, Fan QQ. Effect of different anesthesia depth based on bispectral index of EEG on inflammatory response and postoperative cognitive function in elderly patients undergoing laparoscopic surgery. Hainan Med J 2019;30:2490-2493.

[30] Yue MM, Zhang YL, Wang S, et al. The effect of different BIS values on the early postoperative cognitive function and S100β protein in elderly patients undergoing abdominal surgery. J Clin Anesthesio 2016;32:109-113.

[31] Quan C, Chen J, Luo Y, et al. BIS-guided deep anesthesia decreases short-term postoperative cognitive dysfunction and peripheral inflammation in elderly patients undergoing abdominal surgery. Brain Behav 2019;9:e01238.

[32] Hou R, Wang H, Chen L, et al. POCD in patients receiving total knee replacement under deep vs light anesthesia: A randomized controlled trial. Brain Behav 2018;8:e00910.

[33] Punjasawadwong Y, Chau-In W, Laopaiboon M, et al. Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. Cochrane Database Syst Rev 2018;5:Cd011283.

[34] Deiner S, Luo X, Silverstein JH, et al. Can Intraoperative Processed EEG Predict Postoperative Cognitive Dysfunction in the Elderly? Clin Ther 2015;37:2700-2705.

[35] Dustin Boone M, Lin HM, Liu X, et al. Processed intraoperative burst suppression and postoperative cognitive dysfunction in a cohort of older noncardiac surgery patients. J Clin Monit Comput 2022;36:1433-1440.

[36] Wang X, Chen X, Wu F, et al. Relationship between postoperative biomarkers of neuronal injury and postoperative cognitive dysfunction: A meta-analysis. PLoS One 2023; 18:e0284728.

[37] Yu Z, Bin Z, Min W. Effects of Awake Bispectral Index on Postoperative Cognitive Function in the Elderly. Chin J Rehabil Theory Pract 2013;19:671-673.

[38] Tu M, Zhang Q, Liu X. Influence of Narcotrend-Assisted Anesthesia In-Depth Monitor on

Cognitive Impairment of Elderly Patients under General Anesthesia. Comput Math Methods Med 2022;2022:2866188.

[39] Li DF, Zeng QG, Liang HN, et al. Clinical Analysis of Using Narcotrend EEG Monitoring the Effects of Different Anesthesia Depths on POCD Occurrence and S100β Protein Level. Med Recapitulate 2014;20:2851-2853.

[40] Qiu YS, Xu Q. Accuracy of narcotrend index in monitoring depth of anesthesia in diabetics: a case report. Chin Med Sci J 2014;29:251-252.

[41] Chen W, Zhong S, Ke W, et al. The effect of different depths of anesthesia monitored using Narcotrend on cognitive function in elderly patients after VATS lobectomy. Am J Transl Res 2021;13:11797-11805.

[42] Yang J, Li P, Tang XN. Research Progress of Anesthesia-related Measures to Prevent Postoperative Cognitive Dysfunction in Elderly Patients Undergoing Hip Joint Surgery. Med Recapitulate 2019;25:2457-2462.

[43] Kang ZM, Chen RS, Su CS, et al. Comparison of IoC and EEG Dual-frequency Index Monitoring of Different Anesthesia Depth on Postoperative Cognitive Impairment in Patients with Bowel Cancer. Chin Foreign Med Res 2020;18:32-34.

[44] Viertiö-Oja H, Maja V, Särkelä M, et al. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiol Scand 2004;48:154-161.

[45] Cotae AM, Ţigliş M, Cobilinschi C, et al. The Impact of Monitoring Depth of Anesthesia and Nociception on Postoperative Cognitive Function in Adult Multiple Trauma Patients. Medicina (Kaunas) 2021;57:408.

[46] Hao HZ. The correlation between EEG spectrum pattern and postoperative cognitive dysfunction in elderly patients. Air Force Medical University 2018.

[47] Tarasova I, Trubnikova O, Kupriyanova DS, et al. Cognitive functions and patterns of brain activity in patients after simultaneous coronary and carotid artery revascularization. Front Hum Neurosci 2023;17:996359.

[48] Babiloni C, Arakaki X, Azami H, et al. Measures of resting state EEG rhythms for clinical trials in Alzheimer's disease: Recommendations of an expert panel. Alzheimers Dement 2021;17:1528-1553.

[49] Zhang BY, You Y, Yu WK, et al. Characterization of quantitative EEG in patients with post-operative cognitive dysfunction. J Med Res Combat Trauma Care 2019;32:724-728.

[50] Sorger B, Goebel R. Real-time fMRI for brain-computer interfacing. Handb Clin Neurol 2020;168:289-302.

[51] Warbrick T. Simultaneous EEG-fMRI: What Have We Learned and What Does the Future Hold? Sensors (Basel) 2022;22:2262.

[52] Cichy RM, Oliva A. A M/EEG-fMRI Fusion Primer: Resolving Human Brain Responses in Space and Time. Neuron 2020;107:772-781.