Zentime

Perioperative Precision Medicine

Volume 3, Number 1; Mar. 31, 2025

ISSN: 2957-5443
Editor-in-Chief: Lize Xiong
Published by ZENTIME PUBLISHING CORPORATION

Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Expert Consensus https://doi.org/10.61189/447393ljoyfh

Main types, application conditions, and standards of thoracic drainage tubes in peacetime and wartime: An expert consensus

Wangzheqi Zhang[1], Chenglong Zhu[1], Xingzhi Liao[2], Feixiang Wu[3], Hui Chen[4], Wenyun Xu[5], Jinlong Qu[6], Miao Zhou[7], Jinfei Shi[8], Liangqing Lin[9], Shengyun Cai[10], Wenchao Gao[11], Hua Tang[12], Ying Huang[13], Zui Zou[1]

[1]School of Anesthesiology, Naval Medical University, Shanghai 200433, China. [2]Department of Anesthesiology, 904th Hospital of The Joint Logistics Support Force of the PLA, Wuxi 214044, Jiangsu, China. [3]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China. [4]Department of Anesthesiology and Perioperative medicine, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai 200434, China. [5]Department of Anesthesiology, Second Affiliated Hospital of Naval Medical University, Shanghai 200003, China. [6]Department of Emergency and Critical Care, Medicine Second Affiliated Hospital of Naval Medical University, Shanghai 200003, China. [7]Department of Anesthesiology, the Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University, Nanjing 210009, Jiangsu, China. [8]Department of Anesthesiology, Anhui Provincial Hospital of the Armed Police, Hefei 230001, China. [9]Department of Anesthesiology, The First Hospital of Putian City, Teaching Hospital of Fujian Medical University, Putian 351100, Fujian, China. [10]Department of Obstetrics and Gynecology, First Affiliated Hospital of Naval Medical University, Shanghai 200433, China. [11]Department of Colorectal Surgery, Second Affiliated Hospital of Naval Medical University, Shanghai 200003, China. [12]Department of Thoracic Surgery, The Second Affiliated Hospital of Naval University, Shanghai 200003, China. [13]Department of Intensive Care Unit, the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian, Jiangsu 223300, China.

Corresponding authors: Hua Tang, Ying Huang and Zui Zou.

Acknowledgement: This study was funded by the following projects: Shanghai Industrial Collaborative Innovation Project (HCXBCY - 2023 – 041, XTCX - KJ - 2024 - 39, HCXBCY - 2024 – 033), 2024 Basic Medicine Innovation Open Topic (JCKFKT - MS - 002), and the 2024 Annual Pharmaceutical Science and Technology Key Research Project of the China Medicine Education Association (2024KTZ011).

Declaration of conflict of interest: None.

Received January 20, 2025; Accepted February 20, 2025; Published March 31, 2025

Abstract

Thoracic drainage plays a crucial role in both peacetime and wartime clinical medicine, serving as an indispensable method for treating thoracic diseases and managing trauma patients. Whether in routine medical care or in the complex situations of war or military operations, thoracic drainage is essential. This expert consensus aims to clarify the primary uses and appropriate patient populations for different types of thoracic drainage tubes, providing healthcare professionals with a systematic guide for the correct selection and application of drainage tubes in various scenarios, thereby optimizing treatment outcomes. We emphasize the need to establish specific rapid response mechanisms to meet the urgent medical demands of wartime, ensuring timely and effective thoracic drainage even in resource-limited situations. Furthermore, innovation in new technologies and materials is also key to advancing thoracic drainage techniques.

Keywords: Thoracic drainage, drainage tubes, clinical application, wartime medicine, procedural standards

Address correspondence to: Hua Tang, Department of Thoracic Surgery, The Second Affiliated Hospital of Naval University, Shanghai 200003, China. Email: Tangh_mits@163.com. **Ying Huang**, Department of Intensive Care Unit, the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian, Jiangsu 223300, China. Email: huangying5249@163.com. **Zui Zou**, School of Anesthesiology, Naval Medical University, 168 Changhai Road, Shanghai 200433, China. Email: zouzui@smmu.edu.cn.

Introduction

Thoracic drainage occupies an essential position in clinical medicine, both in peacetime and wartime, serving as a crucial intervention for treating thoracic diseases and trauma patients [1, 2]. During peacetime, the primary indications for thoracic drainage include pleural effusion [3]; pneumothorax [4]; and empyema [2, 3, 5-9]. Although thoracic drainage has become a well-established technique in clinical practice, the continually evolving spectrum of thoracic diseases necessitates that healthcare professionals continuously update their knowledge and skills to meet new challenges [10]. In routine medical settings, considerable progress has been made in standardizing and regulating the use of thoracic drainage techniques. However, further optimization is still needed, particularly regarding the refinement of indications, enhancement of therapeutic outcomes, and reduction of complications [7]. In the context of war or military operations other than war, thoracic drainage often needs to address severe chest trauma, hemothorax, and pneumothorax under complex environmental and situational constraints. Managing chest trauma in combat soldiers is notably challenging and urgent; failure to provide timely and effective thoracic drainage can lead to severe or even fatal outcomes. Given the limited medical resources available during wartime, performing thoracic drainage efficiently and safely becomes critically important. Additionally, the complexities and unpredictability of wartime situations demand higher levels of procedural skills, emergency response capabilities, and psychological resilience from medical personnel [6, 11]. Therefore, a systematic exploration and summary of the types of thoracic drainage tubes, their conditions of application, and standardized operational guidelines are not only beneficial for enhancing routine clinical treatment outcomes but are also crucial for guiding the emergency management of trauma during wartime.

The objective of this consensus is to clearly define the main uses and target audiences for different types of thoracic drainage tubes, providing systematic guidelines to assist healthcare providers in the correct selection and application of drainage tubes across various scenarios to optimize treatment outcomes [10]. In addition, specific operating procedures have been developed to meet the emergency needs of wartime medical conditions and to make timely and effective thoracic drainage under resource-limited situations. We analyze in detail the design features, applicable scenarios, and respective advantages and disadvantages of traditional drainage tubes, minimally invasive drainage tubes, and novel catheter devices to help clinicians make the best choice under different clinical conditions and resource constraints. We also analyze the conditions and indications of application of thoracic drainage tubes, which are: pleural effusion, pneumothorax, and the peculiar conditions of wartime management, detailing for each type of drainage tube the applicable scenarios.

Types of thoracic drainage tubes

Traditional drainage tubes

The traditional thoracic drainage tubes are basic tools in current practice and are usually made of silicone or polyvinyl chloride (PVC). This type of tube is characterized by sturdy walls and several side holes, allowing the evacuation of major amounts of liquid or gas effectively. They are mainly indicated for treating of open and closed pleural effusions and for extensive accumulations of pleural gas, following diseases like massive trauma-induced hemothorax or pneumothorax [10].

Traditional drainage tubes have many advantages. First, these tubes are made from materials that can maintain their stability in very harsh conditions, which is important during wartime when doctors face limited medical supplies and challenging environment. Besides, the multi-side hole design guarantees effective drainage [12]. However, the traditional drainage tube also presents several limitations. Firstly, their high invasiveness might contribute to postoperative complications, and the operation requires a very high level of technical skill and stringent aseptic conditions. Their rigid structure may cause discomfort for the patient and can even lead to secondary injuries in the process of placement [12].

Minimally invasive drainage tubes

With the advances in minimally invasive techniques, including thoracic drainage tubes, this has become a focus of considerable clinical interest. The soft and flexible materials (e.g. polyurethane) in the manufacture of these tubes minimize tissue damage at the time of placement. Its ergonomic design allows accurate placement through smaller incisions, thus minimizing trauma and reducing the risk of infection [13-18].

Minimally invasive drainage tubes are suitable for a wide range of indications, especially in cases with stable effusions and small gas accu-

mulations, including patients sensitive to trauma, such as elderly patients or patients with hematological disorders. The main advantages include less discomfort for the patient during placement, and shorter postoperative recovery periods, and finally, fewer complications. It is much easier to operate, more flexible, and minimally invasive compared to the conventional drainage tubes and may be used in combat or resource-constrained environment [18-20].

However, one of the major disadvantages of minimally invasive drainage tubes is their possible lower efficiency in draining large volumes of fluid or gas. The technologies are relatively new, and the relevant equipment used is extremely expensive. Their use in resource-poor regions is further limited by the high levels of technical proficiency and experience required from operators [19].

Innovative catheter devices

Recent development in technology has introduced advanced catheter devices, including those that use antimicrobial materials and intelligent monitoring systems. These devices further enhance performance when used alongside traditional drainage tubes, offering better patient adaptability and postoperative management benefits [21-25].

Novel catheter devices are designed with sensors and automatic control functions that can monitor the condition of drainage in real time and transmit data [21-23, 26, 27]. This facilitates remote the monitoring and treatment adjustments by healthcare professionals. Therefore, such devices will be suitable not only for routine effusions and gas accumulations but also for wartime rapid response and remote medical settings.

The principal benefits of novel catheter devices are their high degree of intelligence, easing the work of health professionals and thus improving patients' safety and comfort [22-24, 26-28]. On the other hand, the costs of development and application are high. They need highly technical maintenance and operational expertise, which limits their wider application [27, 24]. There are also technical problems related to real-time data transmission and the protection of privacy.

In summary, different types of thoracic drainage tubes each have their respective advantages and applicable scenarios. Optimal drainage methods should be selected based on the specific circumstances in both peacetime and wartime to ensure effective and safe treatment. In the future, the integrated application and technological advancements of these thoracic drainage devices in emergency medical environments will further enhance the standards and outcomes of thoracic drainage therapy.

Indications and applications

In clinical practice, chest drainage tubes play a crucial role in managing various pathological conditions [3, 5]. They are particularly indispensable in cases of pleural effusion, pneumothorax, and emergency medical situations during wartime [3, 4, 28, 29]. However, the specific application and indications can vary significantly depending on the context. Making an informed choice and using chest drainage tubes correctly is essential for ensuring patient safety and therapeutic efficacy [12].

Pleural effusion is one of the most common conditions requiring the use of chest drainage tubes. The clinical indications often include heart failure, infectious diseases such as bacterial pleuritis, and malignant tumors such as lung cancer or metastatic breast cancer [30-32]. For these patients, chest drainage can promptly relieve dyspnea and improve lung function. However, there are different contraindications, including severe coagulopathies and localized infections. For such patients, risks and benefits have to be weighed, while considering alternative treatment options where indicated. A chest drainage tube essential in the treatment of pneumothorax is equally [33-36]. When performing thoracentesis, it is imperative to pay close attention to the patient's coagulation function. For patients with abnormal coagulation profiles, specifically those with platelet counts less than 50 × 10^9/L or an INR (International Normalized Ratio) greater than 1.5, the procedure should be cautiously executed under ultrasound guidance to mitigate the risk of bleeding and ensure the safety of the intervention. However, the anticoagulation considerations for thoracentesis suggest that traditionally perceived contraindications such as coagulopathy, thrombocytopenia, and the use of anticoagulant or antiplatelet medications, may not require the treatment of bleeding risk, indicating that patients can safely undergo the procedure without modification of their anticoagulation status. In summary, it is crucial for clinicians to be aware of the risk factors and to employ strategies that enhance procedural safety, recognizing that major complications from thoracentesis are rare [37, 38].

Typically, spontaneous pneumothorax affects young persons who are usually tall and slender

[4]. Although traumatic pneumothorax may not directly relate to rib fractures, it often coincides with the fracture of ribs or lacerations of lung tissues [39-41]. Thus, patients with pneumothorax generally present with sudden chest pain and dyspnea which, in severe cases, may lead to respiratory failure and shock. Observation or needle aspiration may be forms of clinical treatment for a stable simple pneumothorax. The primary treatment options include the insertion of a chest drainage tube for tension pneumothorax and large pneumothorax. At the time of the placement of the tube, strict attention to sterile technique is critical to avoid injury to the lung and infection [39-41].

Chest drainage tubes also play a critical role in wartime scenarios, such as traumatic hemothorax or battlefield emergency care. Combat-related injuries often involve explosions or gunshot wounds that result in either hemothorax or traumatic pneumothorax [42]. Early chest drainage can greatly improve survival. In these environments, providers should be familiar with methods for battlefield emergencies and should know how to carry out a temporary chest drainage procedure [43-45]. Innovations such as high-sealing and minimally invasive drainage tubes possess a great deal of value within the field by offering flexibility where there would normally be restraints from bulky equipment. In addition, during emergency situations such as combat trauma, the placement of chest tubes may be performed under complex environmental conditions that can compromise the maintenance of strict aseptic technique. In such scenarios, whenever feasible, it is imperative to adhere to the principles of asepsis as closely as possible. Should conditions preclude the guarantee of effective asepsis, in accordance with the clinical management guidelines for intravascular catheters, it is recommended that chest tubes be replaced as soon as possible, ideally within 48 hours of insertion, provided the patient's condition permits. This approach is intended to mitigate the risk of infection. This further underscores the critical importance of sterile technique in the process of chest tube insertion [42-44].

In sum, chest drainage tubes are crucial for the treatment of pleural effusion, pneumothorax, and some special wartime conditions. The indications for selection should be appropriate, flexibly adapted to development in clinical practice, follow strict sterility principles, and employ modern equipment-all these are the keys to guarantee successful drainage without complications. While chest drainage technology continues to evolve and research into a variety of special application conditions deepens, the clinical outcomes will be further improved and bring more hope for patient recovery.

Procedural techniques and standards

The standardization of thoracic drainage procedures during both peacetime and wartime is crucial to ensure efficient and safe operations under varying circumstances, since the procedural specifics and skill level directly affect patient outcomes.

Preoperative preparation

Preoperative preparation is pivotal in ensuring the success of thoracic drainage. Initially, a comprehensive evaluation of the patient is essential, encompassing medical history, physical examination, and necessary imaging studies to ascertain the nature and location of the thoracic pathology. A systematic patient assessment significantly increases the success rate but decreases unnecessary trauma to the patients. Besides, adequate psychological support and detailed explanation will alleviate anxiety in patients for better tolerance of the procedure [46-49].

Equipment selection and preparation must be performed strictly in accordance with the standards. Depending on their design features and indications, traditional drainage tubes, minimally invasive tubes, and new catheter devices must be chosen based on the specific case. All instruments should undergo thorough sterilization before use to ensure aseptic conditions and prevent postoperative infections and other complications [9].

Placement technique

The placement of thoracic drainage tubes is a technically demanding procedure requiring a profound understanding of anatomy and extensive clinical experience. The standard procedural steps are as follows:

1. Utilize imaging and surface landmarks to identify the appropriate puncture site, avoiding critical neurovascular structures [9].

2. Apply local anesthesia and make a small incision on the skin with a surgical knife [7, 12, 50, 51].

3. Insert the drainage tube through the incision into the thoracic cavity promptly, ensuring stable and efficient drainage [7, 50].

4. Secure the drainage tube and connect it to a negative pressure device. If feasible, the use of a closed drainage system is recommended to prevent air from entering the thoracic cavity, which could cause pneumothorax or other complications [7, 12, 50, 52].

It is worth noticing that strict following of aseptic techniques is obligatory during the whole treatment to reduce the level of infection risk. Extra attention is given to the angle and depth of placing the tube to avoid unintentional injury of internal organs or further damage [9].

Postoperative management

Management after surgery is crucial to ensure proper working of the drainage tube and to avoid complications [52]. There is a need for regular monitoring of the volume and characteristic of the fluid drained to correctly assess the efficacy of the treatment in a timely manner. Furthermore, close monitoring of the puncture site is necessary to promptly detect signs of infection, subcutaneous emphysema, or other complications, alongside standard care of the drainage tube according to institutional protocol, including dressing changes, at least daily, maintenance of tube patency, and regular inspection of the negative pressure device [53]. Special attention should be given to securing the drainage tube and limiting patient activity to minimize the risk of accidental dislodgement, especially in patients requiring prolonged drainage [52, 53]. In postoperative management, the secure fixation of the thoracic drainage tube is of paramount importance. Appropriate fixation should be tailored to the patient's position; for instance, when the patient is lying supine, the thoracic drainage tube should be fastened securely at the bedside, maintaining a degree of slack to prevent traction or displacement due to movements such as rolling over, thereby enhancing patient comfort. Concurrently, with respect to drainage, it is imperative to closely monitor the color, volume, and nature of the drainage fluid, ensuring that the drainage tube remains unobstructed. Should any drainage impairment be detected, prompt action should be taken to identify the cause and implement the necessary interventions. This may include inspecting for obstructions or kinks in the tube and managing them in accordance with medical protocols.

In summary, standardization of techniques for thoracic drainage and postoperative management enhances the therapeutic results and significantly reduces complications. Standardized peacetime procedures and adaptable wartime responses are essential for ensuring patient safety and the success of treatments. Future efforts should focus on advancing research and training in this area, promoting the adoption of new technologies and materials to continually improve the proficiency of thoracic drainage procedures.

Discussion

In resource-limited settings, particularly under wartime medical conditions, the implementation of thoracic drainage faces numerous challenges. Firstly, it is crucial to establish a rapid response mechanism to ensure effective intervention in the shortest possible time. This includes not only the swift coordination of medical equipment and supplies but also the quick assembly and deployment of specialized medical teams. Flexibility and adaptability are paramount in this process. Medical personnel must possess the ability to perform thoracic drainage under variable and extreme conditions, which raises the bar for both their technical prowess and psychological resilience. Given the urgent need for rapid response, a systematic and ongoing training mechanism for personnel is essential. The constraints on the number of surgeons and technical staff in wartime environments can be mitigated through simulated drills and remote education. Specifically, with the aid of virtual reality technology and tele-mentoring systems, healthcare workers in remote areas can receive timely and effective training, ensuring they have the confidence and capability for actual operations.

The advancement of thoracic drainage technology will greatly depend on the application of new technologies and materials. For instance, progress in nanotechnology could lead to the development of more efficient and less complication-prone new drainage tube materials [54]. Concurrently, the evolution of minimally invasive surgical equipment will make thoracic drainage safer and more convenient, thereby accelerating patient recovery. Additionally, advancements in AI technology can facilitate the intelligent use of drainage tubes, reducing the burden on medical personnel and allowing for more accurate patient data recording, ultimately enhancing the quality and comfort of medical care. While technological progress is significant, continuous clinical trials and evidence accumulation are crucial for the promotion of new technologies. Only by demonstrating the safety and efficacy of new technologies through large-scale clinical trials can they be widely adopted in clinical practice. Hence, emphasis should be placed on foundational and applied research in

the relevant fields, establishing a comprehensive research and medical integration mechanism.

Thoracic drainage, as a vital medical procedure, relies on multidisciplinary collaboration. The close cooperation of various disciplines is especially critical in both peacetime and wartime medical care. For example, surgeons, internists, and emergency physicians need to communicate thoroughly and discuss the patient's condition to devise the most optimal treatment plan. Furthermore, the meticulous management of postoperative care by nursing staff and the assurance of drug supply by pharmacists are key elements in ensuring the success of drainage. In wartime and other special conditions, multidisciplinary collaboration can significantly enhance the overall efficiency of emergency medical response. By establishing interdisciplinary emergency response teams and coordinated workflow processes, resources can be quickly mobilized, enabling the rapid treatment of the injured. The cross-disciplinary cooperation also promotes the integration of medical technologies, such as imaging techniques for the precise placement of drainage tubes, thereby improving the success rate and safety of the procedure [55].

In conclusion, the application of thoracic drainage in both peacetime and wartime necessitates the reinforcement and optimization of techniques and drainage devices. This approach is vital for effectively elevating the application level of thoracic drainage technology and ensuring the provision of the highest quality medical services to patients under various extreme conditions.

Author Contributions: Wangzheqi Zhang and Chenglong Zhu: Conceptualization and initial draft preparation. Xingzhi Liao, Feixiang Wu, Hui Chen, Wenyun Xu, Jinlong Qu, and Miao Zhou: Contributed to clinical data collection and analysis for the manuscript. Jinfei Shi, Liangqing Lin, Shengyun Cai: Participated in reviewing and refining the content on drainage tube applications. Wenchao Gao, Hua Tang, Ying Huang, Zui Zou: Supervised the study, provided crucial guidance, and finalized the manuscript. All authors jointly ensured the quality and accuracy of this expert consensus.

References

[1] Heus C, Mellema JJ, Giannakopoulos GF, et al. Outcome of penetrating chest injuries in an urban level I trauma center in the Netherlands. Eur J Trauma Emerg Surg 2019;45(3):461-465.

[2] Graham DS, Livingston EH. Chest Tubes. JAMA 2019;322(8):792.

[3] Townshend AP, Speake W, Brooks A. Chylothorax. Emerg Med J 2007;24(2):e11.

[4] Kang SN. Rib fractures, pneumothorax, haemothorax and chest drain insertion. Br J Hosp Med (Lond) 2007;68(9):M158-159.

[5] Klopp M, Pfannschmidt J, Dienemann H. [Treatment of pleural empyema]. Chirurg 2008;79(1):83-94; quiz 95-86.

[6] Swiech A, Boddaert G, Daban JL, et al. Penetrating thoracic injuries: a retrospective analysis from a French military trauma centre. BMJ Mil Health 2021;167(1):33-39.

[7] Filosso PL, Guerrera F, Sandri A, et al. Errors and Complications in Chest Tube Placement. Thorac Surg Clin 2017;27(1):57-67.

[8] Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. Cochrane Database Syst Rev 2017;3(3):Cd010651.

[9] Anderson D, Chen SA, Godoy LA, et al. Comprehensive Review of Chest Tube Management: A Review. JAMA Surg 2022;157(3):269-274.

[10] Venuta F, Diso D, Anile M, et al. Chest Tubes: Generalities. Thorac Surg Clin 2017;27(1):1-5.

[11] de Lesquen H, Beranger F, Berbis J, et al. Challenges in war-related thoracic injury faced by French military surgeons in Afghanistan (2009-2013). Injury 2016;47(9):1939-1944.

[12] Munnell ER. Thoracic drainage. Ann Thorac Surg 1997;63(5):1497-1502.

[13] Palleiko BA, Singh A, Strader C, et al. Clinical outcomes and staff satisfaction after adoption of digital chest drainage system for minimally invasive lung resections. J Thorac Dis 2024;16(5):2963-2974.

[14] Stamenovic D, Dusmet M, Schneider T, et al. A simple size-tailored algorithm for the removal of chest drain following minimally invasive lobectomy: a prospective randomized study. Surg Endosc 2022;36(7):5275-5281.

[15] Lee LP, Chiu WK, Chan HB, et al. Minimally invasive chest drain insertion in children. Hong Kong Med J 2011;17(2):137-140.

[16] Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg 2019;55(1):91-115.

[17] Bertoglio P, Guerrera F, Viti A, et al. Chest drain and thoracotomy for chest trauma. J Thorac Dis 2019;11(Suppl 2):S186-S191.

[18] Santoshi RK, Chandar P, Gupta SS, et al. From Chest Wall Resection to Medical Management: The Continued Saga of Parapneumonic

Effusion Management and Future Directions. Cureus 2022;14(1):e21017.
[19] Piazzolla M, Tondo P. Causes, management and treatment of empyema. Minerva Surg 2024;79(2):210-218.
[20] Sen S, Sentürk E, Pabuşcu E, et al. [Minimally invasive approach in the pleural fluids]. Tuberk Toraks 2010;58(1):71-77.
[21] Toth JW, Reed MF, Ventola LK. Chest Tube Drainage Devices. Semin Respir Crit Care Med 2019;40(3):386-393.
[22] Brunelli A, Salati M, Refai M, et al. Evaluation of a new chest tube removal protocol using digital air leak monitoring after lobectomy: a prospective randomised trial. Eur J Cardiothorac Surg 2010;37(1):56-60.
[23] Cerfolio RJ, Varela G, Brunelli A. Digital and smart chest drainage systems to monitor air leaks: the birth of a new era? Thorac Surg Clin 2010;20(3):413-420.
[24] De Waele M, Agzarian J, Hanna WC, et al. Does the usage of digital chest drainage systems reduce pleural inflammation and volume of pleural effusion following oncologic pulmonary resection?-A prospective randomized trial. J Thorac Dis 2017;9(6):1598-1606.
[25] Comacchio GM, Marulli G, Mendogni P, et al. Comparison Between Electronic and Traditional Chest Drainage Systems: A Multicenter Randomized Study. Ann Thorac Surg 2023;116(1):104-109.
[26] Cerfolio RJ, Bryant AS. The benefits of continuous and digital air leak assessment after elective pulmonary resection: a prospective study. Ann Thorac Surg 2008;86(2):396-401.
[27] Varela G, Jiménez MF, Novoa NM, et al. Postoperative chest tube management: measuring air leak using an electronic device decreases variability in the clinical practice. Eur J Cardiothorac Surg 2009;35(1):28-31.
[28] Bozzay JD, Walker PF, Ronaldi AE, et al. Tube Thoracostomy Management in the Combat Wounded. Am Surg 2018;84(8):1355-1362.
[29] Butler FK, Jr., Holcomb JB, Shackelford SA, et al. Management of Suspected Tension Pneumothorax in Tactical Combat Casualty Care: TCCC Guidelines Change 17-02. J Spec Oper Med 2018;18(2):19-35.
[30] Carlucci P, Trigiani M, Mori PA, et al. Competence in pleural procedures. Panminerva Med 2019;61(3):326-343.
[31] Rahman NM, Maskell NA, Davies CW, et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest 2010;137(3):536-543.
[32] Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, et al. Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions: A Randomized Clinical Trial. JAMA 2020;323(1):60-69.
[33] Huggins JT, Maldonado F, Chopra A, et al. Unexpandable lung from pleural disease. Respirology 2018;23(2):160-167.
[34] Medford AR, Maskell N. Pleural effusion. Postgrad Med J 2005;81(961):702-710.
[35] Sorino C, Mondoni M, Lococo F, et al. Optimizing the management of complicated pleural effusion: From intrapleural agents to surgery. Respir Med 2022;191:106706.
[36] Ukeh I, Fang A, Patel S, et al. Percutaneous Chest Tube for Pleural Effusion and Pneumothorax. Semin Intervent Radiol 2022;39(3):234-247.
[37] Cantey EP, Walter JM, Corbridge T, et al. Complications of thoracentesis: incidence, risk factors, and strategies for prevention. Curr Opin Pulm Med 2016;22(4):378-385.
[38] Wiederhold BD, Sharma S, O'Rourke MC. Thoracentesis. Treasure Island (FL). StatPearls Publishing LLC, 2025.
[39] Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest 2001;119(2):590-602.
[40] de Moya M, Brasel KJ, Brown CVR, et al. Evaluation and management of traumatic pneumothorax: A Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surg 2022;92(1):103-107.
[41] Tran J, Haussner W, Shah K. Traumatic Pneumothorax: A Review of Current Diagnostic Practices And Evolving Management. J Emerg Med 2021;61(5):517-528.
[42] Jacoby RC, Battistella FD. Hemothorax. Semin Respir Crit Care Med 2001;22(6):627-630.
[43] Ching JA, Wachtel TL. A simple device to teach tube thoracostomy. J Trauma 2011;70(6):1564-1567.
[44] Monaghan SF, Swan KG. Tube thoracostomy: the struggle to the "standard of care". Ann Thorac Surg 2008;86(6):2019-2022.
[45] Thomas MO, Ogunleye EO. Penetrating chest trauma in Nigeria. Asian Cardiovasc Thorac Ann 2005;13(2):103-106.
[46] Allibone L. Nursing management of chest drains. Nurs Stand 2003;17(22):45-54; quiz 55-46.
[47] Crawford D. Care and nursing management of a child with a chest drain. Nurs Child Young People 2011;23(10):27-34.
[48] Ghazali D, Ilha-Schuelter P, Barbosa S, et al. Interdisciplinary teamwork for chest tube insertion and management: an integrative review. Anaesthesiol Intensive Ther 2021;53(5):456-465.
[49] Sullivan B. Nursing management of patients with a chest drain. Br J Nurs 2008;17(6):388-

393.

[50] Cooke DT, David EA. Large-bore and small-bore chest tubes: types, function, and placement. Thorac Surg Clin 2013;23(1):17-24, v.

[51] Ellis H. The applied anatomy of chest drain insertion. Br J Hosp Med (Lond) 2007;68(3):M44-M45.

[52] Aho JM, Ruparel RK, Rowse PG, et al. Tube Thoracostomy: A Structured Review of Case Reports and a Standardized Format for Reporting Complications. World J Surg 2015;39(11):2691-2706.

[53] Durai R, Hoque H, Davies TW. Managing a chest tube and drainage system. Aorn j 2010;91(2):275-280; quiz 281-273.

[54] Parikh KS, Josyula A, Omiadze R, et al. Nano-structured glaucoma drainage implant safely and significantly reduces intraocular pressure in rabbits via post-operative outflow modulation. Sci Rep 2020;10(1):12911.

[55] Brogi E, Gargani L, Bignami E, et al. Thoracic ultrasound for pleural effusion in the intensive care unit: a narrative review from diagnosis to treatment. Crit Care 2017;21(1):325.

Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Research Article https://doi.org/10.61189/143336qedqgl

Multi-objective teaching improves learning results: A randomized controlled trial

Kai Wang[1], Zhe Zhang[1], Mingling Wang[2], Shiming Feng[3], Huanjia Xue[1], Xiang Huan[1], Liwei Wang[1]

[1]Department of Anesthesiology, [2]Operating Room, [3]Department of Orthopaedics, Xuzhou Clinical College Affiliated to Xuzhou Medical University, Xuzhou 221009, Jiangsu, China.

Corresponding author: Liwei Wang.

Acknowledgement: This work was supported by Young Scientist Fund of National Natural Science Foundation of China (81700078) and Xuzhou Medical Key Talents program (XWRCHT20220051).

Declaration of conflict of interest: None.

Received November 2, 2024; Accepted February 14, 2025; Published March 31, 2025

Highlights

- Training with the multi-objective teaching model significantly improved in perioperative skills of residents.
- Multi-objective teaching model effectively facilitates the acquisition of comprehensive theoretical knowledge in anesthesiology.
- Multi-objective teaching model emphasizes the development of teamwork skills.

Abstract

Objective: The multi-objective teaching model is an educational strategy that aims to promote the holistic development of students through diverse teaching methods and activities. This study explores the application method of multi-objective teaching model in the standardized training of anesthesiology residents in China, aiming to enhance teaching outcomes and cultivate skilled anesthesiologists. **Methods:** A total of 60 anesthesiology residents undergoing standardized training at our center were included in this clinical observation. Participants (n=30/group) were randomly assigned to either the observation group (multi-objective teaching model) or the control group (conventional teaching model). All the participants received training on ultrasound-guided short-axis in-plane and short-axis out-of-plane axillary brachial plexus nerve block. In the control group, the teaching of the two kinds of punctures were carried out separately without comparison of the two or inclusion of additional puncture techniques. In the observation group, the teaching of the two kinds of puncture were integrated, and the experience was summarized and extended to the vascular and nerve puncture requiring similar technology. After the teaching of two different models, the difference of success rates in supraclavicular vein and internal jugular vein punctures were evaluated. **Results:** The observation group demonstrated a significantly shorter puncture and catheter placement time compared to the control group during supraclavicular vein and internal jugular vein puncture procedures (5.19±2.20 minutes vs. 8.35±2.40 minutes, P<0.01), with a higher success rate (76% vs. 64%, P=0.08). The number of mistaken arterial punctures was significantly reduced (4 cases vs. 8 cases, P=0.26). Additionally, both student and mentor evaluations of the multi-objective teaching model were significantly higher than those of the conventional model (student evaluation: 82±11 points vs. 71±9 points, P<0.01; mentor evaluation: 85±9 points vs. 76±7 points, P<0.01). **Conclusion:** The multi-objective teaching model significantly improves perioperative skills and teaching satisfaction among anesthesiology residents. It is an effective educational approach for enhancing anesthesiology training.

Keywords: Multi-objective teaching, anesthesia practice, residents training

Introduction

As continuous improvement of quality of life, there has been a corresponding increase in the demand for high-quality medical services. This requires clinicians to enhance their pro-

Address correspondence to: Liwei Wang, Department of Anesthesiology, Xuzhou Central Hospital, No.199 Jiefang South Road, Quanshan District, Xuzhou 221009, Jiangsu, China. Email: 760020230115@xzhmu.edu.cn.

fessional expertise and technical proficiency to minimize complications and reduce operational errors during perioperative period [1, 2]. The cultivation of competent young physicians, particularly in enhancing their clinical proficiency while ensuring patient safety, has emerged as a critical challenge in contemporary clinical education. While working as a visiting scholar in the Department of Anesthesiology of Dresden Technical University Hospital, Germany, the first author engaged in extensive clinical observations and identified significant differences in residency training approaches between China and Germany. These comparative insights, following systematic analysis and synthesis, have led to the proposition of implementing a multi-objective teaching model in the standardized training of anesthesiology residents in China. This proposed framework aims to provide valuable references for optimizing the cultivation of anesthesiology talents.

As a pivotal specialty in the surgical system, anesthesiology encompasses extensive clinical practices and diverse procedural contents. While various anesthesia centers in China have their specific protocols and guidelines, they generally adhere to the Chinese clinical practice guidelines. Significant conceptual differences exist between Chinese and German approaches to certain clinical operations [3, 4]. For example, in the ultrasound-guided axillary brachial plexus block, the standard practice involves using the short-axis in-plane approach, where the probe is positioned to visualize the neurovascular structures in cross-section, followed by needle insertion parallel to each nerve branch, which is easy to operate and provides direct visualization to prevent neurovascular injury. In contrast, German practitioners employ the short-axis out-of-plane approach, which is more difficult as it requires constant monitoring of the spatial relationship between the needle tip and neurovascular structures. Their explanation is that the axillary brachial plexus limb region is flat and broad, making it an optimal learning platform for out-of-plane perivascular nerve blocks. Their pedagogical rationale is that if trainees cannot master this technique in the most accessible anatomical location, they will be inadequately prepared for more complex procedures.

This educational philosophy extends to advanced epidural anesthesia techniques. German training programs deliberately assign skilled residents to practice thoracic puncture placement using the paramedian approach, despite its increased technical difficulty. This method proves particularly advantageous in challenging cases involving extensive calcification of the ligamentum flavum. Furthermore, despite the widespread availability of video laryngoscopes, German residency programs maintain rigorous daily training with conventional laryngoscopes to enhance residents' proficiency in managing difficult airways. These self-imposed technical challenges in clinical training embody the fundamental principles of the multi-objective teaching model, the core of which involves to incorporate higher-level training elements when residents demonstrate capacity beyond current instructional level [5].

The multi-objective teaching model represents a goal-oriented pedagogical approach that emphasizes the establishment of hierarchical teaching objectives throughout the training process, with corresponding training plans and instructional methodologies developed for each specific goal. This model aims to enhance the pertinence and efficacy of training, ensuring comprehensive acquisition of requisite knowledge and skills [6, 7]. In standardized residency training, we have consistently encountered several challenges: (1) a disparity between theoretical knowledge and practical skills among residents; (2) uneven proficiency across different clinical procedures, and (3) either insufficient challenge for high-performing residents or inadequate support for less proficient ones [8-10]. This dichotomy not only diminishes the motivation of exceptional residents but also poses potential clinical risks due to inaccurate competency assessment of less skilled residents.

To address these issues, we propose to implement multi-objective teaching model in China's standardized anesthesiology training program. In clinical practice, this approach involves: (1) establishing differentiated teaching objectives tailored to residents' competency levels, (2) implementing individualized instruction based on aptitude assessment, (3) recognizing their achievements upon completion of specific procedures, and (4) setting higher objectives for subsequent training phases.

Through this multi-objective teaching, we aim to provide individualized training that not only meets but potentially exceeds the final goals of standardized residency training. For this reason, we have initiated clinical teaching innovations that integrate continuous practice with systematic summarization. These efforts have led to the development of an enhanced training program, complemented by a refined evaluation system and safeguard mechanisms, all designed to ensure the effective implementation and desired outcomes of the multi-objective

Table 1. Comparison of original axillary brachial plexus nerve blocks ($\bar{x}$ ±SD)

	Control group (n=30)	Multi-objective teaching group (n=30)	t/χ^2value	P value
Operating time (min)	6.32±2.30	4.85±1.80	2.76	0.007
Success rate (%)	84	92	13.64	<0.001
Faulty penetration of artery (n)	2	0	2	0.157
Student evaluation (0-100 points)	80±6	92±8	6.58	<0.001
Mentor evaluation (0-100 points)	82±5	92±7	6.36	<0.001

teaching model.

Methods

Participant selection

A total of 60 anesthesiology residents undergoing standardized training at our center were included in this clinical observation. They were randomly assigned to either the observation group (multi-objective teaching model) or the control group (conventional teaching model), with 30 residents in each group. All the participants first received training on ultrasound-guided short-axis in-plane and short-axis out-of-plane axillary brachial plexus nerve block.

Control group

In the control group, training on ultrasound-guided short-axis in-plane and short-axis out-of-plane axillary brachial plexus nerve block was conducted according to the syllabus. Residents first received theoretical instruction on the procedures, including anatomy, ultrasound image recognition, operational steps, and complication prevention. After the theoretical teaching, residents performed simulated operations on mannequins or models to familiarize themselves with the procedures. Under the guidance of experienced instructors, residents observed actual procedures to deepen their understanding of the operational details before their clinical practice. Each resident completed each 15 cases of ultrasound-guided short-axis in-plane and short-axis out-of-plane axillary brachial plexus block to consolidate their learned knowledge and skills (**Table 1**). After each operation, instructors provided immediate feedback, recognizing the well-done procedures and pointing out what can be enhanced or improved, as well as organizing discussions to encourage peer learning.

Multi-objective teaching group

In the multi-objective teaching group, residents were introduced to the short-axis in-of-plane and short-axis out-of-plane axillary brachial plexus nerve block and underwent operation training. Our multi-objective teaching approach mandates that all clinical procedures be based on a comprehensive theoretical understanding, as only through theoretical guidance can we ensure procedural standardization and patient safety.

To achieve this, the multi-objective teaching model incorporates diverse instructional methodologies [11, 12].

• Interactive theoretical sessions: residents are encouraged to engage in questioning and discussions. These sessions systematically cover fundamental anesthesiology principles while incorporating contemporary advancements and evidence-based practices.

• Case-based learning: our curriculum employs authentic clinical cases to bridge theoretical knowledge with practical application. Each case is carefully selected to reflect a spectrum of clinical scenarios, from routine to complex situations. Residents engage in systematic case analysis, identifying key learning points and formulating management strategies.

• Structured group discussion: facilitated by experienced mentors, who initiate topic presentation and guide brainstorming, residents actively explore and discuss the topic, with key insights synthesized. This format promotes collaborative learning, critical thinking, and knowledge integration among residents.

• Mentorship and feedback: mentors play a crucial role in guiding discussions and providing real-time feedback. They ensure that the discussions remain focused, challenge residents to think critically, and provide insights based on their own experiences. Mentors also facilitates the translation of theoretical knowledge into clinical practice, helping residents to understand the practical implications of the theories they learn.

• Continuous assessment system: the program implements a robust evaluation framework that enables residents to monitor their progress and adapt learning strategies, allows mentors assess competency levels of residents at various training stages, ensuring that only those who demonstrate theoretical mastery and passing comprehensive assessments can proceed to clinical practice.

The multi-objective teaching model standardized training through a structured three-phase approach: simulation training, standardized clinical operations, and advanced clinical operations. Mentors outline the skills to be mastered at each stage and introduce the content for the next stage. Upon successfully completing the goals of current stage, residents progress to higher-level training for further development. The program mandates all residents to complete standardized clinical procedure assessments, with advanced clinical operation assessments available for high-performing residents demonstrating exceptional capacity.

Besides, the multi-objective teaching model underscores the importance of team collaboration among anesthesiology residents [13, 14]. Teamwork serves as a practical implementation mechanism for multi-objective teaching. With varying levels of experience within the team, residents can effectively complete tasks at their current stage through mutual discussion, sharing, and other collaborative activities. This helps residents avoid unnecessary pitfalls and risks in clinical practice, preparing for higher-level practice. Emphasizing collaboration among residents not only enhances residents' skills but also significantly improves teaching and work efficiency.

Additionally, the multi-objective teaching model also emphasizes the cultivation of professional quality among residents of anesthesiology, including responsibility, communication skills, and the ability to cope with pressure. The goal is not only to train residents with qualified professional skills but also to shape them into exceptional doctors with noble character, emotional intelligence, and a sense of professional honor, who can fulfill the Hippocratic Oath [15, 16]. The multi-objective teaching model enables residents to continuously improve themselves in practice by means of situation simulation and role-playing. By integrating these elements into the teaching model, this comprehensive approach aims to cultivate well-rounded doctors capable of navigating the complex landscape of medical practice with clinical excellence and ethical integrity. Therefore, this focus on professional ethics and character development constitutes a fundamental component of the multi-objective teaching model.

Both groups underwent training for two consecutive weeks, with each resident performing 15 actual operations. Two weeks later, residents from both groups were trained in ultrasound-guided short-axis plane supraclavicular vein and internal jugular vein catheterization, performing five clinical practices. The average puncture and catheter placement time, success rate, incidence of complications, and evaluations by both the residents and mentors were recorded. Our investigation focused on core anesthesiology procedures, including ultrasound-guided neurovascular puncture, epidural puncture and catheterization, comparing the efficacy of the multi-objective teaching model with conventional approaches, yielding significant comparative data.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.0. The Kolmogorov-Smirnov test was used to check for normality. Normally distributed data were presented as mean ± standard deviation ($\bar{x}$ ±s). Inter-group comparisons were conducted using ANOVA, followed by Bonferroni post-hoc tests for pairwise comparisons. Categorical data were presented as frequencies (percentages) and analyzed using the χ^2 test. A P value of <0.05 was considered statistically significant.

Results

The results showed that compared with the control group, the multi-objective teaching group demonstrated significantly shorter puncture and catheter placement times, higher success rates, and fewer instances of arterial puncture errors during the subsequent supraclavicular and internal jugular vein puncture operations. Additionally, both trainees and instructors rated the multi-objective teaching model significantly higher than the conventional teaching model (**Tables 2-3**).

Discussion

Since 1993, the Ministry of Health issued the Notice on the Implementation of the Trial Measures for the Standardized Training of Clinical Residents, over 30 years have passed since the national realization of standardized and standardized resident training. In this vigorous development of medicine for more than 30 years, the standardized training system for resi-

Table 2. Comparison of supraclavicular vein puncture and placement ($\bar{x}$ ±SD)

	Control group (n= 30)	Multi-objective teaching group (n= 30)	t/χ^2 value	P value
Puncture and catheter placement time (min)	8.35±2.40	5.19±2.20	5.32	<0.001
Success rate (%)	64	76	5.14	0.023
Faulty penetration of artery (n)	16	8	4.44	0.035
Student evaluation (0-100 points)	71±9	82±11	4.24	<0.001
Mentor evaluation (0-100 points)	76±7	85±9	4.15	<0.001

Table 3. Comparison of internal jugular vein puncture and placement ($\bar{x}$ ±SD)

	Control group (n= 30)	Multi-objective teaching group (n= 30)	t/χ^2 value	P value
Puncture and catheter placement time (min)	6.59±2.10	4.73±1.90	3.60	<0.001
Success rate (%)	88	96	6.52	0.011
Faulty penetration of artery (n)	4	0	2	0.157
Student evaluation (0-100 points)	82±8	91±9	4.09	<0.001
Mentor evaluation (0-100 points)	84±7	93±9	4.33	<0.001

dent doctors has trained thousands of qualified clinical doctors. With the development of the times, some issues have gradually emerged in the teaching of resident standardized training, which need to be solved step by step in our practical work. For instance, the problem of increasing the success rate of operations and reducing complications, in the process of standardized training, requires residents to learn related techniques and content in a comprehensive and multi-objective manner within limited practical opportunities. Another issue is the singularity of the training syllabus and goals, which does not reflect "individualized" teaching. In the teaching process, the focus is mostly on meeting the minimum requirements for assessment, and for outstanding residents, there is rarely an expansion of learning content [7]. Additionally, there is a lack of proactive awareness among training mentors and undifferentiated teaching, which fails to set different goals based on the level of residents, leading to "the excellent students being under-challenged and the less capable ones struggling to keep up," thus dampening the motivation and enthusiasm for further learning [17-19]. All of these can be well solved by the multi-objective teaching model.

After comparing the differences in clinical anesthesia teaching practice between China and Germany, out center also made corresponding summaries and explorations. After a period of trial, we found that the multi-objective teaching model has the following advantages.

• Improving the pertinence of training: the multi-objective teaching model can make a personalized training plan according to the specific situation of each resident, to improve the pertinence and effect of training.

• Combination of multiple teaching methods: the multi-objective teaching model combines various teaching methods, allowing residents to better grasp knowledge and skills.

• Timely feedback and adjustment: the multi-objective teaching model focuses on timely feedback and adjustment, enabling residents to promptly understand their learning status and adjust their learning strategies.

• Cultivation of teamwork: the multi-objective teaching model places importance on the cultivation of teamwork, allowing residents to better integrate into teamwork.

• Improving professional ethics: the multi-objective teaching model stresses the development of professional ethics, enabling residents to continuously improve their professional ethics in practice.

The multi-objective teaching model, originally emerging in the foundational theoretical teaching of major universities, has achieved good results. Tian et al. put forward the hierarchical and multi-objective teaching model of Medical Statistics under the conditions of informatization, and adopted different teaching depths and methods among undergraduates, postgrad-

uates and foreign students, which fully aroused the enthusiasm of all kinds of students in learning and significantly improved their academic performance [20]. Sun et al. explored the multi-objective teaching model in the teaching of advanced mathematics, proposing various student-centered teaching methods to adapt to the construction and development of new engineering disciplines, and also achieved the expected teaching results [21]. In the practice of continuing medical education, some scholars have also proposed a stratified teaching method, which involves scientifically stratifying the trainees, developing individualized training programs, and conducting stratified teaching and assessment, thereby embodying the concept of individual differences and precise teaching [22, 23]. This method is part of the multi-objective teaching model we propose, which only advocates "teaching according to the aptitude of the learner" without integrating multi-objectives throughout the entire teaching process. The concept of multi-objective teaching is to provide individualized teaching to residents at different levels at different stages, but during the teaching process, it also sets higher-level requirements so that after completing the current teaching goals, progress can be made toward higher levels. Moreover, the multi-objective concept is not only for residents, but we hope to fully reflect the multi-objective philosophy in the design of the syllabus, the initiative of the mentors, and the aspects of humanities and professional ethics.

One of the limitations of our study is the relatively small sample size of 60 anesthesiology residents. This restricts the generalizability of our findings and may affect the statistical power of our comparisons. The small sample size also limits our ability to draw definitive conclusions about the long-term effects of the multi-objective teaching model on residents' professional development. To address these limitations, future research should aim to include larger and more diverse cohorts of residents from multiple centers. This would enhance the external validity of the findings and allow for more robust statistical analysis. Additionally, longitudinal studies could be conducted to assess the sustained impact of the multi-objective teaching model on residents' skills and professional growth over time.

While this study aimed to explore the application of the multi-objective teaching model in China, it is essential to acknowledge the potential challenges and limitations that may arise when adopting this model. One significant challenge is the differences in healthcare systems and educational infrastructures between Germany and China. The German healthcare system's emphasis on standardized procedures and advanced technology may not be as readily available in all Chinese medical institutions, which could hinder the implementation of certain teaching methods. Additionally, resource constraints, such as the availability of qualified instructors and state-of-the-art equipment, could limit the effectiveness of the multi-objective teaching model in some settings. The disparities in regional development within China mean that not all medical facilities may have the capacity to support this model, particularly in rural or less developed areas.

Conclusions

The multi-objective teaching model has obvious advantages in the training of anesthesiology residents, which can comprehensively improve the theoretical knowledge, clinical skills, teamwork ability and professional quality of residents. Through continuous optimization and improvement of the multi-objective teaching model, the quality of resident training can be enhanced, contributing more to the development of the medical profession.

Author contributions: Kai Wang contributed to the conception of the study. Kai Wang and Zhe Zhang performed the experiment. Mingling Wang and Shiming Feng contributed significantly to analysis and manuscript preparation. Kai Wang performed the data analyses and wrote the manuscript. Huanjia Xue and Xiang Huan helped perform the analysis with constructive discussions. Liwei Wang supervised the study and contributed to the analysis through constructive discussions.

References

[1] Zhu J, Li W, Chen L. Doctors in China: improving quality through modernisation of residency education. Lancet (London, England) 2016;388(10054):1922-1929.

[2] Powell DE, Carraccio C. Toward Competency-Based Medical Education. N Engl J Med 2018;378(1):3-5.

[3] Bogdanyova S, Lermann J, de Sousa Mendes M, et al. Becoming a resident in Germany: an experience-based practical guideline. Arch Gynecol Obstet 2015;291(2):457-460.

[4] Wick A, Beckmann A, Nemeth A, et al. Cardiac surgery residents training in Germany-Status quo and future prospects. J Thorac Cardiovasc Surg 2020;159(2):579-587.

[5] Chinai SA, Guth T, Lovell E, et al. Taking Advantage of the Teachable Moment: A Review

of Learner-Centered Clinical Teaching Models. West J Emerg Med 2018;19(1):28-34.
[6] Li E. On the Multi-objective, Individualized and Stratified Teaching Mode of Public English Courses in Higher Vocational Colleges. Front Educ Res 2022;5(18):73-77.
[7] Huang PH, Haywood M, O'Sullivan A, et al. A meta-analysis for comparing effective teaching in clinical education. Med Teach 2019;41(10):1129-1142.
[8] Levy KL, Grzyb K, Heidemann LA, et al. Enhancing Resident Education by Embedding Improvement Specialists Into a Quality and Safety Curriculum. J Grad Med Educ 2023;15(3):348-355.
[9] Massagli TL, Zumsteg JM, Osorio MB. Quality Improvement Education in Residency Training: A Review. Am J Phys Med Rehabil 2018;97(9):673-678.
[10] Madhusoodanan V, Bitran J, Towe M, et al. Financial and Business Literacy Among Urology Residents: Is this a Problem and How Can We Better Prepare Residents for their Careers? Curr Urol Rep 2024;25(9):207-214.
[11] Zhao YY, Zhang TT, Li LH, et al. Application of online to offline teaching mode in the training of non-anesthesiology residents in the department of anesthesiology: a randomized, controlled trial. Front Med (Lausanne) 2024;11(2296-858X):1329538.
[12] Yang L, Li W, Zou J, et al. The application of the spot the difference teaching method in clinical skills training for residents. BMC Med Educ 2022;22(1):542.
[13] Behling F, Adib SD, Haas P, et al. Not taught in medical school but needed for the clinical job - leadership, communication and career management skills for final year medical students. BMC Med Educ 2024;24(1):1126.
[14] Hochberg MS, Berman RS, Pachter HL. Professionalism in Surgery: Crucial Skills for Attendings and Residents. Adv Surg 2017;51(1):229-249.
[15] Hwang I. Medical Humanism in the Post-human Era: A Critical Examination of its Past, Present, and Future. Uisahak 2023;32(1):115-145.
[16] Katsnelson G, Brenna CTA. The heart of anaesthesiology: revitalising humanism in the age of technology. Br J Anaesth 2024;132(1):1-4.
[17] Oladeji LO, Ponce BA, Worley JR, et al. Mentorship in Orthopedics: A National Survey of Orthopedic Surgery Residents. J Surg Educ 2018;75(6):1606-1614.
[18] Silver CM, Yuce TK, Clarke CN, et al. Disparities in Mentorship and Implications for US Surgical Resident Education and Wellness. JAMA Surg 2024;159(6):687-695.
[19] Schultz KS, Hess DT, Sachs TE, et al. A Structured Mentorship Elective Deepens Personal Connections and Increases Scholarly Achievements of Senior Surgery Residents. J Surg Educ 2021;78(2):405-411.
[20] Tian JD, Wu FF, Wen C. Effects of a teaching mode combining SimBaby with standardized patients on medical students' attitudes toward communication skills. BMC Med Educ 2022;22(1):825.
[21] Sun J, Liu T, Li H. Study on the status and problems of teaching system of "medical advanced mathematics": data based on a research of 11 universities in China. BMC Medical Educ 2024;24(1):36.
[22] Chen M, Ye L, Weng Y. Blended teaching of medical ethics during COVID-19: practice and reflection. BMC Med Educ 2022;22(1):361.
[23] Zhao MY. The effect of different teaching methods on the problem solving ability of nursing students was compared. Cardiovascular Disease Electronic J Integr Tradit Chin West Med 2018;6(10):166-168.

Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Review Article https://doi.org/10.61189/619896szhnms

Research progress on mitochondrial autophagy in sepsis-related acute lung injury

Kecheng Zhai[1,2], Yangmengna Gao[1,2], Yu Xiang[1,2], Jiameng Liu[1,2], Shangping Fang[1,2]

[1]School of Anesthesiology, [2]Anesthesia Laboratory and Training Center, Wannan Medical College, Wuhu 241002, Anhui Province, China.

Corresponding author: Shangping Fang.

Acknowledgement: This work was supported by the National College Student Innovation and Entrepreneurship Project (202310368016) and Anhui Province College Student Innovation and Entrepreneurship Project (S202310368027).

Declaration of conflict of interest: None.

Received October 24, 2024; Accepted January 8, 2025; Published March 31, 2025

Highlights

- Mitochondrial autophagy is essential for maintaining mitochondrial health by selectively degrading damaged mitochondria. This process involves two main pathways: ubiquitin-dependent and ubiquitin-independent autophagy.
- Sepsis causes organ dysfunction due to infection, with acute lung injury (ALI) being a common secondary condition. ALI is characterized by excessive inflammation in the lungs, leading to mitochondrial dysfunction.
- Understanding the mechanisms of mitochondrial autophagy can provide new insights for treating sepsis-associated ALI. Continued research could identify novel therapeutic targets to improve outcomes for patients with ALI and sepsis.
- In the early stages of sepsis-related ALI, mitochondrial autophagy is enhanced. In severe or prolonged cases, excessive mitochondrial autophagy may occur. In the later stages, particularly in severe or chronic cases, mitochondrial autophagy may be impaired or completely lost.
- Mitochondrial autophagy holds therapeutic potential for the perioperative assessment and management of sepsis-related ALI. Further investigation into this potential is warranted.

Abstract

Sepsis is a systemic inflammatory response syndrome caused by infection, leading to acute lung injury and acute respiratory distress syndrome, which are common life-threatening complications in intensive care units. Mitochondrial autophagy, a process that selectively removes damaged mitochondria, is essential for maintaining the stability of the intracellular environment and cellular function. In recent years, the role of mitochondrial autophagy in sepsis-associated acute lung injury and acute respiratory distress syndrome has garnered significant attention. This review summarizes the research progress of mitochondrial autophagy in sepsis-associated acute lung injury and acute respiratory distress syndrome, focusing on its mechanism, influencing factors, and potential therapeutic agents.

Keywords: Mitochondrial autophagy, sepsis, acute lung injury

Introduction

Sepsis is a clinical complication resulting from infection-induced organ dysfunction, which is associated with high morbidity and mortality rates. It is the leading cause of death among critically ill patients [1]. In 2017, there were approximately 48.9 million cases of sepsis globally, with 11 million sepsis-related deaths, accounting for 19.7% of all deaths worldwide [2]. Acute lung injury (ALI) is the most common disease associated with sepsis [3]. ALI is characterized by an excessive inflammatory response in the lungs, involving immune cell activation, secretion of pro-inflammatory mediators, and disruption of membrane function [4]. During

Address correspondence to: Shangping Fang, Anesthesia Laboratory and Training Center, Wannan Medical College, No. 22, Wenchang West Road, Higher Education Park, Wuhu 241002, Anhui Province, China. E-mail: 20180041@wnmc.edu.cn.

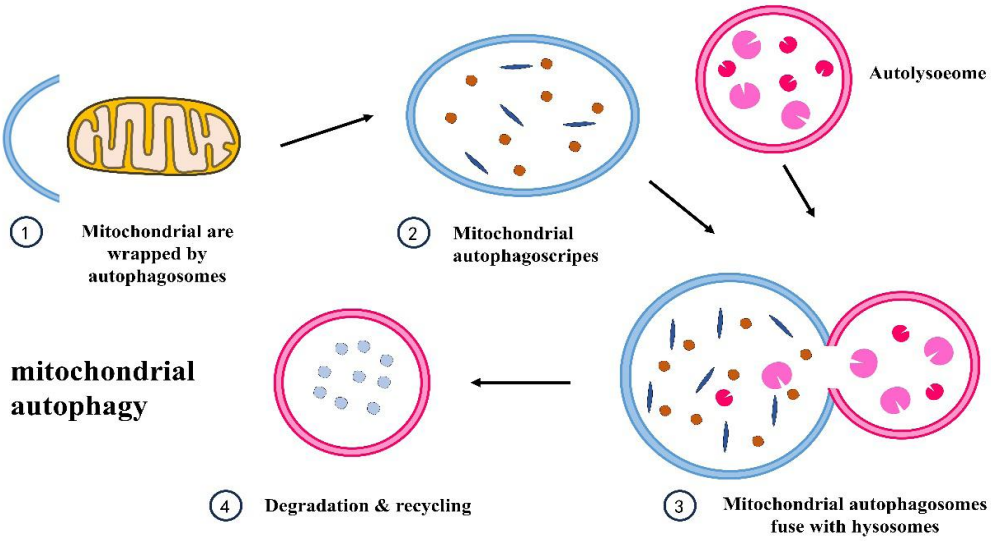


Figure 1. The main processes of mitophagy.

ALI, mitochondria lose their ability to regulate calcium and reactive oxygen species (ROS) levels, leading to excessive mitochondrial free radical leakage, mitochondrial DNA damage, and the production of mitochondrial ROS. The accumulation of mitochondrial ROS activates NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasomes, which in turn trigger caspase-1-dependent pyroptosis, a key driver of cellular focal death in ALI [5]. In contrast, mitochondrial autophagy, a cellular process that maintains mitochondrial health, plays a critical role in the development and progression of ALI. In this process, damaged mitochondria due to pathological conditions such as hypoxia, oxidative stress, and inflammation, are selectively cleared and degraded, thereby maintaining homeostasis and normal lung tissue function [6]. This paper aims to elucidate the molecular mechanisms underlying mitochondrial autophagy and the pathogenesis of mitochondrial autophagy disorders in sepsis-associated ALI, providing new insights for clinical treatment strategies.

Mitochondrial autophagy

Mitochondria are bioenergetic, biosynthetic, and signaling organelles that play a key role in stress perception, enabling cellular adaptation to environmental changes [7]. Many mitochondrial components and metabolites act as damage-associated molecular patterns, promoting inflammation when released into the cytoplasmic lysate or extracellular space. To prevent harmful inflammatory responses, organisms employ mitochondrial quality control systems, including the autophagic clearance of damaged mitochondria. However, when these systems' homeostatic capacity is overwhelmed or defective, mitochondria-induced inflammatory responses may become pathogenic and contribute to the development of various diseases such as neurodegenerative diseases, cardiovascular diseases, cancers, metabolic disorders, and infections [8].

Mitochondrial autophagy plays a critical role in eliminating dysfunctional mitochondria and maintaining mitochondrial homeostasis. Under conditions such as starvation, hypoxia, and endoplasmic reticulum stress, the damaged mitochondria depolarize and lose membrane potential, initiating selective autophagy of damaged mitochondria [9]. These mitochondria are engulfed by autophagosomes, forming mitochondrial autophagosomes (a double-membrane structure). The mitochondrial autophagosomes then fuse with lysosomes to form autophagic lysosomes, where the mitochondrial contents are degraded by lysosomal enzymes and subsequently recycled for cellular use (**Figure 1**).

Molecular mechanisms of mitochondrial autophagy

Mitochondrial autophagy mechanisms are generally divided into two categories: ubiquitin-dependent mitophagy and ubiquitin-independent mitophagy.

Ubiquitin-dependent mitochondrial autophagy

As the name suggests, ubiquitin-dependent autophagy involves the extensive ubiquitination of damaged mitochondria, which are then recognized and degraded by the proteasome. Current research highlights that the Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)/Parkin pathway is a key regulator

of mitochondrial autophagy [10]. PINK1 is a mitochondrial serine/threonine protein kinase containing mitochondrial-targeting sequences that direct its localization to the mitochondria. Under normal mitochondrial conditions, PINK1 is imported into mitochondria via the outer membrane translocase and inner membrane translocase complexes. Upon translocation to the inner mitochondrial membrane, PINK1 is cleaved by matrix processing peptidase and the inner membrane protease PINK1/Phosphoglycerate mutase family member 5 (PGAM5)-associated rhodopsin-like protease and subsequently degraded by the proteasome via the N-terminal rule pathway.

However, when mitochondria are damaged, the loss of membrane potential prevents PINK1 from being imported into the inner membrane, causing the accumulation of PINK1 on the outer mitochondrial membrane (OMM), where it undergoes autophosphorylation and dimerization. PINK1 then phosphorylates Parkin, activating its E3 ubiquitin ligase activity. In turn, Parkin ubiquitinates several outer membrane proteins, forming polyubiquitin chains that are subsequently phosphorylated by PINK1, acting as "eat-me" signals for the core autophagy machinery [11].

Parkin, an E3 ubiquitin ligase encoded by the PARK2 gene, ligates ubiquitin to substrate proteins. The proteasome recognizes the ubiquitin tag and degrades the substrate protein. After mitochondrial damage, PINK1 promotes a conformational change of Parkin into an active E3 ubiquitin ligase, which enhances mitochondrial autophagy. Simultaneously, PINK1 phosphorylates ubiquitin on substrates of OMM proteins, recruiting Parkin from the cytoplasm to the OMM with high affinity. Activated Parkin can then ubiquitinate OMM proteins, such as mitofusin-2 and voltage-dependent anion channel 1, promoting the formation of polyubiquitin chains [12]. Parkin ubiquitinates OMM protein substrates, and PINK1 phosphorylates the ubiquitin chains, further recruiting and activating Parkin, thus creating a feedback loop that amplifies the phosphorylation of ubiquitin [13].

Autophagy receptors, including Optineurin, NDP52, Sequestosome 1 (SQSTM1)/p62, NBR1, and TAX1BP1, recognize the phosphorylated polyubiquitin chains and anchor the mitochondria to autophagosomes by binding to microtubule-associated protein 1 light chain 3 (LC3). The formation of autophagosomes is initiated by the recruitment of autophagy initiation factors, including unc-51-like autophagy-activating kinase 1 (ULK1), WD-repeat domain, phosphatidylinositol-interacting protein 1 (WIPI1), and double FYVE domain-containing protein 1 (DFCP1). TANK-binding kinase 1 is also activated and phosphorylated, enhancing the binding of NDP52 and Optineurin to polyubiquitinated chains. These receptors further promote the synthesis of phagocytic vesicles, the precursors of autophagosomes that eventually fuse with lysosomes for degradation, by recruiting key autophagosome biogenesis components (WIPI1, ULK1, and DFCP1) [5].

In addition to the PINK1-Parkin pathway, other E3 ubiquitin ligases, such as Gp78, SMURF1, Siah1, MUL1, and ARIH1, play roles in regulating mitochondrial autophagy independent of Parkin [14-18]. Once localized on the mitochondrial surface, these ligases generate ubiquitin chains. The autophagy receptor then recognizes the phosphorylated polyubiquitin chains and anchors the mitochondria to the autophagosome by binding to LC3 (**Figure 2**).

Ubiquitin-independent mitochondrial autophagy

Ubiquitin-independent mitochondrial autophagy is mediated by a set of OMM proteins that act as mitochondrial autophagy receptors. These include Nip3-like protein X (NIX), BCL2-interacting protein 3-like (BNIP3L), BCL2-interacting protein 3 (BNIP3), and FUN14 Domain Containing 1 (FUNDC1). These receptors initiate mitochondrial autophagy by binding directly to LC3, independent of ubiquitylation. NIX, also known as BNIP3L, was initially identified when mice with NIX gene deletion exhibited impaired maturation of reticulocytes, leading to the accumulation of excessive mitochondria due to defective mitochondrial autophagy, ultimately resulting in anemia [19]. NIX proteins can directly bind to LC3 through their BH3 structural domain, inducing mitochondrial autophagy. Similarly, BNIP3, which also contains the BH3 structural domain, shares 56% homology with NIX, as both belong to a subfamily of the anti-apoptotic B-cell lymphoma-2 (Bcl-2) family, characterized by the presence of the BH3 domain [20]. BNIP3 deficiency significantly inhibits mitochondrial autophagy, thereby exacerbating apoptosis. FUNDC1, another conserved mitochondrial autophagy receptor, also binds to LC3. It induces Parkin-independent mitochondrial autophagy in mammalian cells under hypoxic conditions (**Figure 2**).

Mitochondrial autophagy and sepsis-related ALI

Under normal physiological conditions, cells

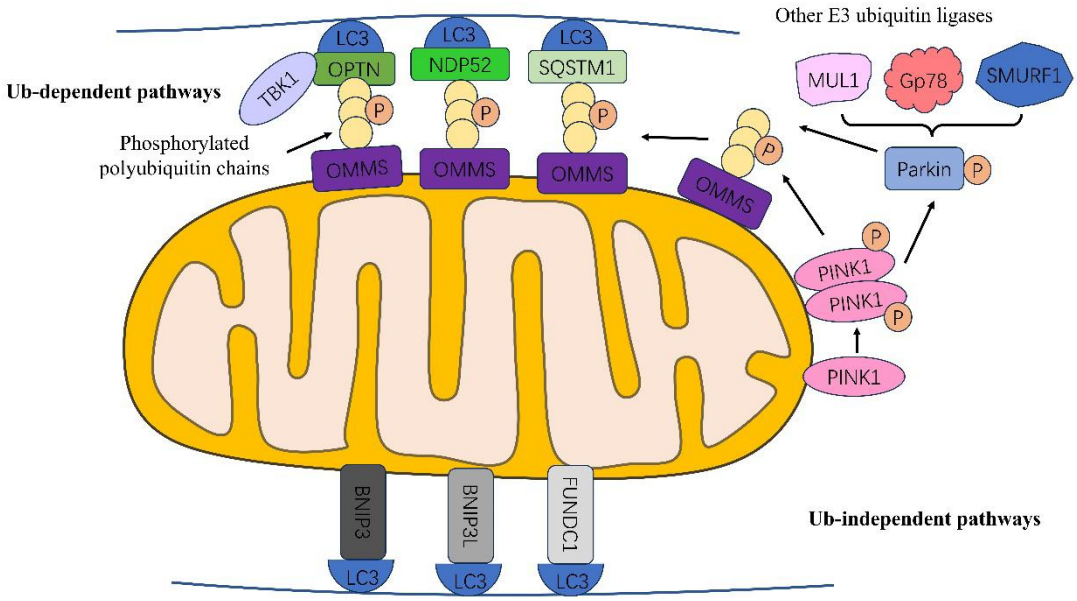


Figure 2. Mechanistic overview of mitophagy. TBK1, TANK-Binding Kinase 1; OPTN, Optineurin; NDP52, Nuclear dot protein 52; SQSTM1, Sequestosome 1; LC3, Microtubule-associated protein 1 light chain 3; PINK1, PTEN-induced kinase 1; Parkin, Parkinson protein 2, E3 ubiquitin protein ligase; MUL1, Mitochondrial E3 Ubiquitin Ligase 1; Gp78, Glucose-regulated protein 78; SMURF1, SMAD specific E3 ubiquitin protein ligase 1; BNIP3, BCL2 Interacting Protein 3; BNIP3L, BCL2 Interacting Protein 3 Like; FUNDC1, FUN14 Domain Containing 1.

maintain mitochondrial quality control through basal levels of autophagy. In lung cells, mitochondrial autophagy plays a crucial role in eliminating damaged or dysfunctional mitochondria, thereby preventing the accumulation of ROS and preserving cellular homeostasis. This basal process is regulated by the PINK1/Parkin pathway and mitochondrial autophagy receptors, such as NIX/BNIP3, ensuring lung tissue integrity and proper cellular function, especially in lung epithelial and endothelial cells.

The balance between pro- and anti-inflammatory mediators governs the progression of the inflammatory response following sepsis-associated ALI. Maintaining this balance is critical for controlling infection in patients. However, disruption of this homeostasis results in the release of pro-inflammatory mediators into the bloodstream, triggering a broader inflammatory cascade and organ dysfunction [21]. The lungs, which play a key role in gas exchange by oxygenating the blood and removing carbon dioxide, receive large amounts of blood and are therefore primary sites for the diffusion of inflammatory mediators during sepsis [22]. These mediators can cause inflammation, increase oxidative stress, and damage lung tissue.

Oxidative phosphorylation in mitochondria is a major route for ROS production due to abnormal electron leakage [23]. Although mitochondria possess antioxidant proteins that can neutralize ROS, excessive ROS production can impair the endothelial barrier function in the pulmonary vasculature and alveolar epithelium, leading to immune cell infiltration (e.g., neutrophils) secretion of cytotoxic substances, and mitochondrial damage. In sepsis-induced ALI, ultrastructural changes in mitochondria include reduced mitochondrial mass, disrupted cristae, and extensive mitochondrial swelling [24]. Mitochondrial autophagy removes aged and damaged mitochondria through selective segregation and lysosomal degradation, thus limiting ROS production.

ROS-induced mtDNA damage reduces mitochondrial membrane potential and leads to protein and lipid oxidation. In response, mitochondrial autophagy plays a critical role in maintaining mitochondrial function and facilitating DNA repair. Inhibition of mitochondrial autophagy has been shown to disrupt mitochondrial Ca2+ homeostasis, impair ATP production, and hinder DNA repair [25]. Suliman et al. observed widespread activation of mitochondrial autophagy in the alveolar region of a mouse model of S. aureus-induced pneumonia [26]. This quality control process contributes to the removal and replacement of damaged mitochondria in lung cells, thereby enhancing cell survival and supporting alveolar function.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates mitochondrial quality, cytoprotective gene expression, oxidative stress response, and an-

ti-inflammatory and anti-apoptotic processes through downstream factors such as HO-1, Bcl-2, and B-cell lymphoma-extra large [27]. Nrf2 activation has been shown to reduce ROS production by counteracting mitochondrial toxins and regulating the production of reduced glutathione [28]. Additionally, Nrf2 deficiency may impair mitochondrial fatty acid oxidation and reduce ATP production [29]. Downregulation of classical autophagy during sepsis exacerbates lung inflammation, whereas Nrf2 activation promotes mitochondrial autophagy in the alveolar region. This process selectively removes damaged mitochondria, facilitates tissue repair, and enhances cell survival, thereby attenuating sepsis-induced ALI and acute respiratory distress syndrome (ARDS).

However, in cases of severe or prolonged ALI, excessive mitochondrial autophagy can lead to cellular energy depletion and impaired mitochondrial biogenesis. This can cause significant mitochondrial loss, leading to further energy deficits and worsening tissue damage. Additionally, excessive mitochondrial autophagy also releases damage-associated molecular patterns, which amplify the inflammatory response, creating a vicious cycle of damage. In the later stages of ALI, especially in severe or chronic cases, mitochondrial autophagy may become impaired or absent. This dysfunction leads to the accumulation of damaged mitochondria, increased ROS production, mitochondrial fragmentation, and heightened oxidative stress.

The time-dependent effects of mitochondrial autophagy in ALI are critical for determining the trajectory of injury and recovery. Early mitochondrial autophagy is protective, as it removes damaged mitochondria and limits inflammation. However, in cases of prolonged or excessive injury, mitochondrial autophagy becomes detrimental, leading to mitochondrial depletion and further tissue damage. In the later stages, mitochondrial autophagy dysfunction exacerbates oxidative stress and hinders cellular repair. Therefore, interventions should focus on enhancing mitochondrial autophagy during the early stages of injury, controlling excessive mitochondrial autophagy during prolonged injury, and restoring mitochondrial autophagy function in later stages to optimize recovery from sepsis-induced ALI and ARDS [30].

PINK1/Parkin signaling pathway and acute lung injury

The PINK1/Parkin pathway is a classical mitochondrial autophagy signaling pathway that plays a crucial role in ALI. It has been shown that resveratrol may improve ALI in mice by inhibiting the activation of NLRP3 inflammasomes, activating the PINK1/Parkin pathway, and promoting mitochondrial autophagy [31]. In the absence of PINK1, mitochondrial autophagy was found to be halted; However, resveratrol upregulated the expression of PINK1, Parkin, Beclin-1, autophagy-related 5, and microtubule-associated protein 1A/1B light chain 3B, which enhanced mitochondrial autophagy, offering a new therapeutic target for the treatment of ALI.

In addition, targeting Bcl-2 family proteins, including Bcl-2 and Bad, can modulate sepsis-induced ALI through the PINK1/Parkin signaling pathway. The anti-apoptotic role of Bcl-2 in various apoptotic cells and animal models is well documented [32, 33]. Bad, an upstream member of the Bcl-2 family, acts as a sensor for cellular stress, injury, infection, growth factor deprivation, and apoptosis [34]. Bad is a BH3-like protein that interacts with Bcl-2. The BH1-BH4 structural domains of Bcl-2 form a hydrophobic groove that binds to Bad, thus regulating autophagy. Hollville et al. demonstrated that Bcl-2 family proteins can inhibit mitochondrial autophagy by preventing translocation of Parkin to depolarized mitochondria in HeLa and HEK293T cells [35]. Additionally, in lipopolysaccharide (LPS) induced A549 cell injury and ALI in mice, elevated apoptosis, enhanced mitochondrial autophagy, decreased Bcl-2 expression, increased Bad expression, and activation of the PINK1/Parkin pathway were observed in both cells and lung tissues [36]. However, both Bcl-2 overexpression and Bad knockdown attenuated LPS-induced injury, inhibited apoptosis and mitochondrial autophagy, and increased survival. Furthermore, Bcl-2 family proteins regulated mitochondrial autophagy by promoting the recruitment of Parkin from the cytoplasm to the mitochondria through direct protein interactions [36].

Mitochondrial autophagy receptors and sepsis-related ALI

Mitochondrial autophagy, mediated by receptors such as BNIP3L/NIX and FUNDC1, plays a vital role in mitochondrial network reorganization during cell differentiation. Knockdown of these receptors during differentiation results in sustained mitochondrial fission and the formation of damaged mitochondria, thereby increasing the likelihood of cell death [37]. Therefore, mitochondrial autophagy receptors are crucial for maintaining the integrity and health of lung cells.

FUNDC1

FUNDC1 is a key receptor for mitochondrial autophagy. Under normoxic conditions, FUNDC1 is phosphorylated by the protein kinase Src, which reduces the interaction between phosphorylated FUNDC1 and LC3, thereby inhibiting FUNDC1-mediated mitochondrial autophagy [38]. Under hypoxic conditions, reduced Src kinase activity leads to decreased phosphorylation of FUNDC1, which facilitates the interaction between dephosphorylated FUNDC1 and LC3, thus promoting mitochondrial autophagy [39]. Autophagy is significantly increased in response to ALI, especially in alveolar epithelial cells and pulmonary vascular endothelial cells. Study has shown that autophagy is activated under hypoxic conditions, making FUNDC1 a key molecule involved in hypoxia-induced mitochondrial autophagy [40]. Following LPS intervention, the autophagic proteins FUNDC1 and LC3-II were elevated, while P62/SQSTM1 was decreased. Notably, FUNDC1 knockdown led to reduced autophagic activity and more severe lung injury following LPS treatment. Additionally, survival curves showed higher mortality in FUNDC1 knockout mice compared to wild-type mice [41].

BNIP3 and BNIP3L/NIX

BNIP3 and BNIP3L/NIX are target genes of HIF-1 that contain an LC3-interacting region. These proteins can recruit LC3 autophagosomes, thereby inducing mitochondrial autophagy [42]. BNIP3 has a dual function: it can promote cell survival through autophagy or induce cell death via apoptosis. BNIP3 binds to Bcl-2, which activates Beclin1 from its inactivation complex, initiating autophagy.

Simultaneously, BNIP3 interacts with mitochondrial fusion protein optic atrophy 1 to promote cell death [43]. It has been shown that inhibiting mitochondrial autophagy and apoptosis by regulating BNIP3 with the HIF-1α inhibitor YC-1 significantly reduces lung injury [44]. Luo et al. identified the transcription factor Runt-related transcription factor 1 (RUNX1) as a key regulator of injury-induced mitochondrial autophagy, and silencing RUNX1 significantly suppressed the expression of BNIP3 and BNIP3L. RUNX1 regulates mitochondrial autophagy by upregulating the expression of mitochondrial autophagy receptors [45]. The transcription factor RUNX1 plays a crucial role in regulating injury-induced mitochondrial autophagy, activating autophagy, and reducing lung inflammation during acute lung injury.

Drugs that ameliorate ALI by affecting mitochondrial autophagy

Small molecule modulators of mitochondrial autophagy are valuable pharmacological tools for studying complex biological processes and translating these insights into potential therapeutic drugs. In recent years, pharmacological modulation of mitochondrial autophagy has demonstrated promising therapeutic effects in ALI models. This section summarizes the current state of research on mitochondrial autophagy modulators, analyzes the available chemical tools, and discusses their advantages, limitations, and current applications (**Table 1**).

Nrf2 inducers

Radish thiols

Radish thiols, found in broccoli, possess significant biological properties. One of the most notable compounds is Sulforaphane, a potent natural activator of the transcription factor Nrf2, which is known for its antioxidant and anti-inflammatory effects [46]. Sulforaphane promotes the translocation of Nrf2 to the nucleus, thereby activating the expression of antioxidant enzymes. Interestingly, activation of the Nrf2 pathway can also increase the production of ROS in mitochondria. At moderate levels, ROS acts as a signaling molecule for mitochondrial damage and trigger the process of mitochondrial autophagy. In an animal model of oleic acid-induced ARDS, sulforaphane treatment was found to reduce lung injury and exert a protective effect by upregulating NRF2 expression [47].

P62-mediated mitochondrial autophagy inducer (PMI)

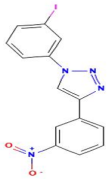
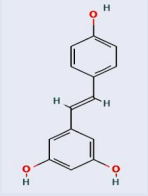
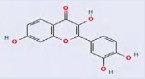
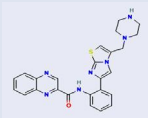
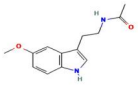
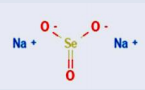
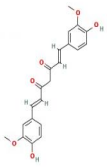
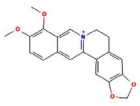
A recently developed compound, PMI, enhances the expression and signaling of the autophagy adaptor protein P62/SQSTM1, which drives mitochondria into autophagy [48]. PMI promotes the accumulation of Nrf2 by targeting the interactions between Nrf2 and Keap1, specifically inhibiting Keap1 and thus enhancing Nrf2 signaling. Importantly, PMI does not disrupt the mitochondrial membrane potential. Therefore, PMI holds significant therapeutic potential for the treatment of ALI [49].

Sirtuin 1 (SIRT1) activators

Sirtuin 1

SIRT1 is a deacetylase that regulates various

Table 1. Drugs that ameliorate acute lung injury by affecting mitochondrial autophagy

Classification	Names	Chemical structure	Mechanisms	Advantages or limitations	References
Nrf2 inducers	Sulforaphane		Activating Nrf2	Low specificity	[46, 47]
	PMI		Inhibiting Keap1	High therapeutic potential; High specificity	[48, 49]
SIRT1 activators	Resveratrol		Activating SIRT1 directly	Low specificity; Induction of general autophagy	[50, 51]
	Fisetin		Activating SIRT1 directly	Non-toxic, and safe	[52, 53]
	SRT1720		Activating SIRT1 directly	High therapeutic potential	[54, 55]
Amine hormone	Melatonin		Upregulating the PINK1/Parkin pathway and inhibiting mTOR.	Strong antioxidant; High safety	[56-59]
Superoxide generator	Sodium selenite		Activating MUL1, ROS-dependent, down-regulation of MCL-1	Nontoxic Low cost Se Supplementation	[17, 60-64]
Natural products	Curcumin		Activation via AMPK	Reference effect on the treatment of ALI. Risk of contact dermatitis with excessive intake	[65-68]
	Berberine		Upregulating the PINK1/Parkin pathway	High therapeutic potential	[69-74]

Note: Nrf2, Nuclear factor erythroid 2-related factor 2; PMI, P62-mediated mitochondrial autophagy inducer; SIRT1, Sirtuin 1; PINK1, PTEN-induced kinase 1; mTOR, mechanistic target of rapamycin; MUL1, Mitochondrial E3 Ubiquitin Ligase 1; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; MCL-1, Myeloid Cell Leukemia-1ALI, acute lung injury; Se, Selenium.

cellular activities by controlling biological processes such as gene expression, DNA repair, metabolism, and mitochondrial function. SIRT1 may initiate mitochondrial autophagy by promoting the deacetylation and subsequent activation of LC3. The most well-known activators of SIRT1 include resveratrol, fexofenadine, and synthetic small molecules such as SRT1720.

Resveratrol

Resveratrol, a polyphenolic compound found in grapes and peanuts, is renowned for its potent antioxidant and anti-inflammatory properties [50]. As a well-known activator of SIRT1, resveratrol, upon activation, regulates mitochondrial autophagy through deacetylation. Specifically, SIRT1 activates the PINK1/Parkin pathway, enhancing selective mitochondrial autophagy (mitophagy). Additionally, SIRT1 also facilitates autophagy by deacetylating ULK1, a core protein of the autophagy initiation complex [51]. As an antioxidant, resveratrol reduces the production of ROS, which, in excess, can dam-

age mitochondria and inhibit autophagy. By lowering ROS levels, resveratrol helps maintain normal mitochondrial function and promotes the removal of damaged mitochondria, thereby protecting cells from oxidative stress.

Fisetin

Fisetin is a natural flavonoid found abundantly in vegetables and fruits, known for its broad pharmacological effects, including anti-inflammatory, anti-apoptotic, antioxidant, anti-tumor, and anti-angiogenic properties [52]. SIRT1 facilitates the recognition and clearance of damaged mitochondria by deacetylating proteins such as PINK1 and Parkin. Studies have shown that Fisetin enhances the stability and activity of PINK1, enabling its accumulation on damaged mitochondria, which subsequently recruits Parkin [53]. Parkin then ubiquitinates the damaged mitochondria, marking them for degradation. Additionally, laccasein has been reported to accelerate the clearance of damaged mitochondria by modulating this pathway [53].

SRT1720

SRT1720 is a synthetic small molecule that activates SIRT1, leading to the deacetylation of PINK1, which stabilizes PINK1 and enhances its accumulation and function on damaged mitochondria [54]. The accumulation of PINK1 on the mitochondrial membrane recruits Parkin, an E3 ubiquitin ligase, which tags damaged mitochondria for degradation via the autophagy pathway. By deacetylating PINK1, SRT1720 enhances the activity of the PINK1/Parkin pathway, thereby facilitating mitochondrial autophagy (mitophagy) [55].

Melatonin

Melatonin is an indole heterocyclic compound primarily secreted by the pineal gland, well known for its role in regulating sleep and its anti-inflammatory, antioxidant, anti-aging, and antiviral properties [56]. Additionally, melatonin also regulates mitochondrial autophagy. Melatonin inhibits excessive mitochondrial autophagy through the PINK1/Parkin pathway [57]. It reduces oxidative damage and improves mitochondrial function by directly scavenging ROS and activating antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. Furthermore, melatonin promotes mitochondrial repair and autophagy by upregulating endogenous antioxidants like glutathione. In addition, Melatonin inhibits the mechanistic target of rapamycin (mTOR) pathway, a critical regulator of cell growth, proliferation, and autophagy inhibition. By inhibiting mTOR, melatonin activates the autophagic process, promoting mitochondrial clearance and renewal [58]. Several clinical studies have investigated melatonin's potential in treating ALI and ARDS, focusing on its antioxidant, anti-inflammatory, and lung function-improving effects [59]. These studies have shown that melatonin improves oxygenation, reduces inflammatory markers, and decreases lung injury. However, direct clinical evidence supporting melatonin's ability to ameliorate ALI through mitochondrial autophagy remains limited. Despite this, melatonin has been found to improve the survival rate of critically ill septic patients in the perioperative period.

Sodium selenite

Selenium is an essential trace element in the human body, and its deficiency is linked to a variety of diseases. It has been reported that serum or plasma selenium levels tend to decrease early in critically ill patients, especially those suffering from sepsis or infectious shock [60]. Research has demonstrated that sodium selenite activates the E3 ubiquitin ligase MUL1 in a ROS-dependent manner. This activation recruits ULK1 to the mitochondria, promoting its autophagic degradation [17]. Additionally, intravenous sodium selenite has been found to restore lung antioxidant capacity, modulate the inflammatory response, and significantly improve respiratory mechanics in ALI patients [61]. Several clinical studies have shown that low selenium status may be associated with the severity of ALI, and that selenium supplementation, including sodium selenite, can help reduce oxidative stress and inflammation [62-64]. By improving the antioxidant defense system, sodium selenite contributes to the alleviation of lung injury [61].

Natural products

Curcumin

Curcumin, a polyphenolic compound found in the rhizome of Curcuma longa, regulates the expression of receptor complexes, growth factors, and other molecules, ultimately exerting biological functions such as anti-inflammatory, anticancer, and antidiabetic properties [65]. In an energy-deficient state (e.g., low ATP/AMP ratio), AMP-activated protein kinase (AMPK) is activated. AMPK, a crucial intracellular energy-sensing enzyme of the serine/threonine kinase family, plays a crucial role in maintaining energy homeostasis by regulating various meta-

bolic pathways [66]. Activated AMPK promotes autophagy by mTOR, a key cellular signaling protein that regulates biological processes such as cell growth, proliferation, and protein synthesis. mTOR exists in two complexes: mTORC1 and mTORC2, with mTORC1 playing a significant role in regulating mitochondrial autophagy. mTORC1 inhibits autophagy by phosphorylating and tinhibiting ULK1, a core enzyme that initiates mitochondrial autophagy [67]. Additionally, the mitochondrial permeability transition pore (mPTP) plays a crucial role in cellular stress responses, particularly during apoptosis and autophagy. Excessive mPTP opening leads to a loss of mitochondrial membrane potential, triggering apoptosis. Curcumin regulates mPTP by reducing oxidative stress, potentially preventing excessive opening and thereby preserving mitochondrial function and integrity. Moderate mPTP opening may also promote mitochondrial autophagy, and curcumin enhances mitochondrial quality control by optimizing this process [68].

Berberine

Berberine, a quaternary isoquinoline alkaloid isolated from several herbs such as Coptis chinensis, is known for its wide range of biological activities, including anti-inflammatory, anti-diarrheal and anti-colitis effects. It is characterized by low toxicity and low cost, which has led to its widespread use over-the-counter for treating gastroenteritis, colitis, diarrhea, and dysentery [69]. Berberine can be oxidized to 8-oxoberberine, known as oxyberberine, which has been found to possess superior anti-inflammatory, antifungal, and antiarrhythmic properties compared to berberine [70]. Studies have shown that oxyberberine reduces lung injury by inhibiting inflammatory responses through the inhibition of Parkin/Pink1-mediated mitochondrial autophagy in LPS-induced ALI [71, 72]. Additionally, oxyberberine inhibits LPS-induced translocation of Parkin1 from cytoplasm to mitochondria [73]. Furthermore, berberine activates the AMPK/mTOR pathway and promotes mitochondrial autophagy by inhibiting mTOR [74].

Conclusion

Modulating mitochondrial autophagy to ameliorate ALI has emerged as a promising therapeutic strategy in recent years. While enhancing mitochondrial autophagy has shown promise in alleviating ALI in animal models, several challenges remain in translating this strategy into effective clinical treatments. For instance, pharmacological interventions targeting mitochondrial autophagy—such as those involving the PINK1/Parkin pathway or small molecules that modulate autophagy factors—are not yet widely used in clinical practice. Moreover, the selectivity and potential side effects of these drugs require comprehensive evaluation. To effectively regulate mitochondrial autophagy, the development of highly selective, low-toxicity drugs remains a critical research focus. Currently, several small molecules capable of modulating mitochondrial autophagy, either by enhancing the PINK1/Parkin pathway or by modulating the NIX/BNIP3 pathway, have been identified. Future advancements may lead to the development of small molecule drugs targeting these pathways, with their efficacy in treating acute lung injury further validated through animal studies.

Author Contributions: Kecheng Zhai performed the conception of the study; Yangmengna Gao, Yu Xiang, and Jiameng Liu contributed to the literature and collection of materials; Kecheng Zhai and Yangmengna Gao contributed to material analysis and manuscript writing; Yu Xiang and Jiameng Liu reviewed and refined the manuscript.Shangping Fang Oversaw the overall planning and coordination of the research, as well as the final review of the manuscript.

References

[1] Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810.

[2] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200-211.

[3] Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest 2012;122(8):2731-2740.

[4] Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol 2005;33(4):319-327.

[5] Mohsin M, Tabassum G, Ahmad S, et al. The role of mitophagy in pulmonary sepsis. Mitochondrion 2021;59:63-75.

[6] Ng MYW, Wai T, Simonsen A. Quality control of the mitochondrion. Dev Cell 2021;56(7):881-905.

[7] Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell 2012;148(6):1145-1159.

[8] Doblado L, Lueck C, Rey C, et al. Mitophagy

in Human Diseases. Int J Mol Sci 2021;22(8):3903.
[9] Xu Y, Shen J, Ran Z. Emerging views of mitophagy in immunity and autoimmune diseases. Autophagy 2019;16(1):3-17.
[10] Jie L, Dongming Y, Zhiping L, et al. PINK1/Parkin-mediated mitophagy in neurodegenerative diseases. Ageing Res Rev 2022;84:101817.
[11] Dong Y, Zhuang XX, Wang YT, et al. Chemical mitophagy modulators: Drug development strategies and novel regulatory mechanisms. Pharmacol Res 2023;194(0):106835.
[12] Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. Nat Cell Biol 2018;20(9):1013-1022.
[13] Pickles S, Vigié P, Youle RJ. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. Curr Biol 2018;28(4):R170-R185.
[14] Alan P, Vandevoorde KR, Joshi B, et al. Basal Gp78-dependent mitophagy promotes mitochondrial health and limits mitochondrial ROS. Cell Mol Life Sci 2022;79(11):565.
[15] Dagar N, Kale A, Steiger S, et al. Receptor-mediated mitophagy: An emerging therapeutic target in acute kidney injury. Mitochondrion 2022;66:82-91.
[16] Abd Elghani F, Safory H, Hamza H, et al. SIAH proteins regulate the degradation and intramitochondrial aggregation of PINK1: Implications for mitochondrial pathology in Parkinson's disease. Aging Cell 2022;21(12):e13731.
[17] Li J, Qi W, Chen G, et al. Mitochondrial outer-membrane E3 ligase MUL1 ubiquitinates ULK1 and regulates selenite-induced mitophagy. Autophagy 2015;11(8):1216-1229.
[18] Howard M, Erickson J, Cuba Z, et al. A secretory form of Parkin-independent mitophagy contributes to the repertoire of extracellular vesicles released into the tumour interstitial fluid in vivo. J Extracell Vesicles 2022;11(7):e12244.
[19] Schweers RL, Zhang J, Randall MS, et al. NIX is required for programmed mitochondrial clearance during reticulocyte maturation. Proc Natl Acad Sci U S A 2007;104(49):19500-19505.
[20] Zhang J, Ney PA. Role of BNIP3 and NIX in cell death, autophagy, and mitophagy. Cell Death Differ 2009;16(7):939-946.
[21] Bosmann M, Ward PA. The inflammatory response in sepsis. Trends Immunol 2012;34(3):129-136.
[22] Park I, Kim M, Choe K, et al. Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. Eur Respir J 2019;53(3):
[23] Susana C. Mitochondrial uncoupling, ROS generation and cardioprotec-tion. Biochim Biophys Acta Bioenerg 2018;1859(9):1800786.
[24] Tran M, Tam D, Bardia A, et al. PGC-1α promotes recovery after acute kidney injury during systemic inflammation in mice. J Clin Invest 2011;121(10):4003-4014.
[25] Dan X, Babbar M, Moore A, et al. DNA damage invokes mitophagy through a pathway involving Spata18. Nucleic Acids Res 2020;48(12):6611-6623.
[26] Suliman HB, Kraft B, Bartz R, et al. Mitochondrial quality control in alveolar epithelial cells damaged by S. aureus pneumonia in mice. Am J Physiol Lung Cell Mol Physiol 2017;313(4):L699-L709.
[27] Vomund S, Schäfer A, Parnham MJ, et al. Nrf2, the Master Regulator of Anti-Oxidative Responses. Int J Mol Sci 2017;18(12):2772.
[28] Zhu L, Zhang Q, Hua C, et al. Melatonin alleviates particulate matter-induced liver fibrosis by inhibiting ROS-mediated mitophagy and inflammation via Nrf2 activation. Ecotoxicol Environ Saf 2023;268:115717.
[29] Li Y, Feng YF, Liu XT, et al. Songorine promotes cardiac mitochondrial biogenesis via Nrf2 induction during sepsis. Redox Biol 2020;38:101771.
[30] Ajoolabady A, Chiong M, Lavandero S, et al. Mitophagy in cardiovascular diseases: molecular mechanisms, pathogenesis, and treatment. Trends Mol Med 2022;28(10):836-849.
[31] Wu D, Zhang H, Li F, et al. Resveratrol alleviates acute lung injury in mice by promoting Pink1/Parkin-related mitophagy and inhibiting NLRP3 inflammasome activation. Biochim Biophys Acta Gen Subj 2024;1868(7):130612
[32] Zhang Y, Yang X, Ge X, et al. Puerarin attenuates neurological deficits via Bcl-2/Bax/cleaved caspase-3 and Sirt3/SOD2 apoptotic pathways in subarachnoid hemorrhage mice. Biomed Pharmacother 2019;109:726-733.
[33] Jin L, Chen Y, Cheng D, et al. YAP inhibits autophagy and promotes progression of colorectal cancer via upregulating Bcl-2 expression. Cell Death Dis 2021;12(5):457.
[34] Puthalakath H, Strasser A. Keeping killers on a tight leash: transcriptional and post-translational control of the pro-apoptotic activity of BH3-only proteins. Cell Death Differ 2002;9(5):505-512.
[35] Hollville E, Carroll RG, Cullen SP, et al. Bcl-2 family proteins participate in mitochondrial quality control by regulating Parkin/PINK1-dependent mitophagy. Mol Cell 2014;55(3):451-466.
[36] Zhang Z, Chen Z, Liu R, et al. Bcl-2 Proteins

Regulate Mitophagy in Lipopolysaccharide-Induced Acute Lung Injury via PINK1/Parkin Signaling Pathway. Oxid Med Cell Longev 2020;2020:6579696.

[37] Lampert MA, Orogo AM, Najor RH, et al. BNIP3L/NIX and FUNDC1-mediated mitophagy is required for mitochondrial network remodeling during cardiac progenitor cell differentiation. Autophagy 2019;15(7):1182-1198.

[38] Li K, Xia X, Tong Y. Multiple roles of mitochondrial autophagy receptor FUNDC1 in mitochondrial events and kidney disease. Front Cell Dev Biol 2024;12:1453365.

[39] Liu L, Feng D, Chen G, et al. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 2012;14(2):177-185.

[40] Li G, Li J, Shao R, et al. FUNDC1: A Promising Mitophagy Regulator at the Mitochondria-Associated Membrane for Cardiovascular Diseases. Front Cell Dev Biol 2021;9:788634.

[41] Pan P, Chen J, Liu X, et al. FUNDC1 Regulates Autophagy by Inhibiting ROS-NLRP3 Signaling to Avoid Apoptosis in the Lung in a Lipopolysaccharide-Induced Mouse Model. Shock (Augusta, Ga.) 2021;56(5):773-781.

[42] Zhang Y, Liu D, Hu H, et al. HIF-1α/BNIP3 signaling pathway-induced-autophagy plays protective role during myocardial ischemia-reperfusion injury. Biomed Pharmacother 2019;120:109464.

[43] Liu KE, Frazier WA. Phosphorylation of the BNIP3 C-Terminus Inhibits Mitochondrial Damage and Cell Death without Blocking Autophagy. PloS one 2015;10(6):e0129667.

[44] Jiang H, Huang Y, Xu H, et al. Inhibition of hypoxia inducible factor-1α ameliorates lung injury induced by trauma and hemorrhagic shock in rats. Acta Pharmacol Sin 2012;33(5):635-643.

[45] Tang X, Zhong L, Tian X, et al. RUNX1 promotes mitophagy and alleviates pulmonary inflammation during acute lung injury. Signal Transduct Target Ther 2023;8(1):288.

[46] Mahn A, Castillo A. Potential of Sulforaphane as a Natural Immune System Enhancer: A Review. Molecules 2021;26(3):752.

[47] Sun Z, Niu Z, Wu S, et al. Protective mechanism of sulforaphane in Nrf2 and anti-lung injury in ARDS rabbits. Exp Ther Med 2018;15(6):4911-4915.

[48] East D, Fagiani F, Crosby J, et al. PMI: a ΔΨm independent pharmacological regulator of mitophagy. Chem Biol 2014;21(11):1585-1596.

[49] Georgakopoulos ND, Frison M, Alvarez MS, et al. Reversible Keap1 inhibitors are preferential pharmacological tools to modulate cellular mitophagy. Sci Rep 2017;7(1):10303.

[50] Conte E, Fagone E, Fruciano M, et al. Anti-inflammatory and antifibrotic effects of resveratrol in the lung. Histol Histopathol 2014;30(5):523-529.

[51] Kang RR, Sun Q, Chen KG, et al. Resveratrol prevents benzo(a)pyrene-induced disruption of mitochondrial homeostasis via the AMPK signaling pathway in primary cultured neurons. Environ Pollut 2020;265(Pt A):115331.

[52] Pal HC, Pearlman RL, Afaq F. Fisetin and Its Role in Chronic Diseases. Adv Exp Med Biol 2016;928:213-244.

[53] Jia S, Xu X, Zhou S, et al. Fisetin induces autophagy in pancreatic cancer cells via endoplasmic reticulum stress- and mitochondrial stress-dependent pathways. Cell Death Dis 2019;10(2):142.

[54] Ma Z, Tang P, Dong W, et al. SIRT1 alleviates IL-1β induced nucleus pulposus cells pyroptosis via mitophagy in intervertebral disc degeneration. Int Immunopharmacol 2022;107:108671.

[55] Jiang T, Liu E, Li Z, et al. SIRT1-Rab7 axis attenuates NLRP3 and STING activation through late endosomal-dependent mitophagy during sepsis-induced acute lung injury. Int J Surg 2024;110(5):2649-2668.

[56] Reiter RJ, Tan DX, Rosales-Corral S, et al. Mitochondria: Central Organelles for Melatonin's Antioxidant and Anti-Aging Actions. Molecules 2018;23(2):509.

[57] Zeng L, He J, Liu C, et al. Melatonin Attenuates Ropivacaine-Induced Apoptosis by Inhibiting Excessive Mitophagy Through the Parkin/PINK1 Pathway in PC12 and HT22 Cells. Inflammation 2022;45(2):725-738.

[58] Shen YQ, Guerra-Librero A, Fernandez-Gil BI, et al. Combination of melatonin and rapamycin for head and neck cancer therapy: Suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. J Pineal Res 2017;64(3).

[59] Kang JY, Xu MM, Sun Y, et al. Melatonin attenuates LPS-induced pyroptosis in acute lung injury by inhibiting NLRP3-GSDMD pathway via activating Nrf2/HO-1 signaling axis. Int Immunopharmacol 2022;109:108782.

[60] Manzanares W, Moreira E, Hardy G. Pharmaconutrition revisited for critically ill patients with coronavirus disease 2019 (COVID-19): Does selenium have a place? Nutrition 2020;81:110989.

[61] Mahmoodpoor A, Hamishehkar H, Shadvar K, et al. The Effect of Intravenous Selenium on Oxidative Stress in Critically Ill Patients with Acute Respiratory Distress Syndrome. Immunol Invest 2018;48(2):147-159.

[62] Kočan L, Vašková J, Vaško L, et al. Selenium

adjuvant therapy in septic patients selected according to Carrico index. Clin Biochem 2014;47(15):44-50.

[63] Hafizi M, Kalanaky S, Fakharzadeh S, et al. Beneficial effects of the combination of BCc1 and Hep-S nanochelating-based medicines on IL-6 in hospitalized moderate COVID-19 adult patients: a randomized, double-blind, placebo-controlled clinical trial. Trials 2023;24(1):720.

[64] Mahmoodpoor A, Hamishehkar H, Shadvar K, et al. The Effect of Intravenous Selenium on Oxidative Stress in Critically Ill Patients with Acute Respiratory Distress Syndrome. Immunol Invest 2019;48(2):147-159.

[65] Hay E, Lucariello A, Contieri M, et al. Therapeutic effects of turmeric in several diseases: An overview. Chem Biol Interact 2019;310:108729.

[66] Carling D. AMPK signalling in health and disease. Curr Opin Cell Biol 2017;45:31-37.

[67] Wang X, Jia J. Magnolol improves Alzheimer's disease-like pathologies and cognitive decline by promoting autophagy through activation of the AMPK/mTOR/ULK1 pathway. Biomed Pharmacother 2023;161:114473.

[68] Zheng Q, Liu H, Zhang H, et al. Ameliorating Mitochondrial Dysfunction of Neurons by Biomimetic Targeting Nanoparticles Mediated Mitochondrial Biogenesis to Boost the Therapy of Parkinson's Disease. Adv Sci (Weinh) 2023;10(22):e2300758.

[69] Li C, Ai G, Wang Y, et al. Oxyberberine, a novel gut microbiota-mediated metabolite of berberine, possesses superior anti-colitis effect: Impact on intestinal epithelial barrier, gut microbiota profile and TLR4-MyD88-NF-κB pathway. Pharmacol Res 2019;152:104603.

[70] Li CL, Tan LH, Wang YF, et al. Comparison of anti-inflammatory effects of berberine, and its natural oxidative and reduced derivatives from Rhizoma Coptidis in vitro and in vivo. Phytomedicine 2019;52:272-283

[71] Li X, Bai Y, Ma Y, et al. Ameliorating effects of berberine on sepsis-associated lung inflammation induced by lipopolysaccharide: molecular mechanisms and preclinical evidence. Pharmacol Rep 2023;75(4):805-816.

[72] Liu H, You L, Wu J, et al. Berberine suppresses influenza virus-triggered NLRP3 inflammasome activation in macrophages by inducing mitophagy and decreasing mitochondrial ROS. J Leukoc Biol 2020;108(1):253-266.

[73] Zhao R, Wang B, Wang D, et al. Oxyberberine Prevented Lipopolysaccharide-Induced Acute Lung Injury through Inhibition of Mitophagy. Oxid Med Cell Longev 2021;2021:6675264.

[74] Khater SI, Almanaa TN, Fattah DMA, et al. Liposome-Encapsulated Berberine Alleviates Liver Injury in Type 2 Diabetes via Promoting AMPK/mTOR-Mediated Autophagy and Reducing ER Stress: Morphometric and Immunohistochemical Scoring. Antioxidants (Basel) 2023;12(6):1220.

Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Review Article https://doi.org/10.61189/554453zztqhf

Cardiac injury induced by obstructive jaundice: A comprehensive review

Chunyang Li[1,2], Mingyao Chen[2], Dedong Zhang[3], Tianying Xu[2], Zhenmeng Wang[4]

[1]School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China. [2]School of Anesthesiology, Naval Medical University/Second Military Medical University, Shanghai 200433, China. [3]Pharmacy Department, Xiamen Special Service Convalescent Center, Xiamen 361001, Fujian Province, China.[4]Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University/Second Military Medical University, Shanghai 200438, China.

Corresponding authors: Zhenmeng Wang and Tianying Xu.

Declaration of conflict of interest: None.

Received January 7, 2024; Accepted March 13, 2025; Published March 31, 2025

Highlights

- Elevated bile acid concentrations impair myocardial structure and function by disrupting mitochondrial integrity and acting on TGR5 and FXR receptors.
- Endotoxins contribute to cardiovascular dysfunction by exacerbating systemic inflammation, primarily via NF-κB activation and increased levels of pro-inflammatory cytokines such as TNF-α.
- Reactive oxygen species alter cardiac electrophysiology by modulating L-type calcium channels and reversing Na^+/Ca^{2+} exchanger activity, leading to contractile dysfunction. Excessive nitric oxide disrupts vascular tone regulation.
- Autophagy is activated through the AMPK-mTOR-ULK1 signaling pathway, while apoptosis-driven myocardial injury is mediated by caspase activation and the Bax/Bcl-2 protein family.
- Appropriate preoperative management, anesthetic selection, and the application of traditional Chinese medicine can alleviate cardiac injury associated with obstructive jaundice.

Abstract

Obstructive jaundice can lead to systemic multi-organ complications, with the heart being one of the most critically affected organs. This review summarizes recent insights into the mechanisms of cardiac injury induced by obstructive jaundice, including bile acid toxicity, inflammatory responses, oxidative stress, nitric oxide dysregulation, endotoxemia, apoptosis, and autophagy. Currently, no specific treatment protocol exists for this condition. However, appropriate anesthetic choices, traditional Chinese herbal medicine, and optimized perioperative management have shown potential in mitigating myocardial damage. This review provides a detailed discussion of these aspects.

Keywords: Obstructive jaundice, cardiac injury, bile acids, mechanisms

Introduction

Obstructive jaundice (OJ) is a common clinical condition caused by partial or complete blockage of intrahepatic or extrahepatic bile ducts, most often due to bile duct stones, inflammatory hyperplasia, or tumors. These conditions lead to impaired bile drainage from the liver. In severe cases, patients with OJ develop jaundice, characterized by yellowing of the skin and eyes due to elevated bilirubin levels in the blood. OJ is associated with high morbidity and mortality rates. Previous studies have reported that the surgical mortality rate for patients with OJ can reach 18% and approximately 8%-10% of surgical patients develop acute renal failure, of whom 70–80% eventually succumb to the condition [1]. OJ can cause multi-organ damage, affecting the liver, kidneys, heart, intestines, brain, and immune system [2-4]. A

Address correspondence to: Zhenmeng Wang, Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University/Second Military Medical University, 225 Changhai Road, Yangpu District, Shanghai 200438, China. Tel: +86-13022130811. E-mail: wzm11998@163.com. **Tianying Xu**, School of Anesthesiology, Naval Medical University, 800 Xiangyin Road, Yangpu District, Shanghai 200433, China. Tel: +86-021 81872029. E-mail: xutianying@smmu.edu.cn.

comprehensive understanding of OJ is crucial for optimizing treatment and improving patient outcomes. To study OJ and its complications, various experimental models have been developed, among which bile duct ligation (BDL) is widely used to simulate OJ and related pathophysiological changes [5].

Cardiac injury is a significant complication of OJ, contributing to increased morbidity and mortality. OJ is associated with various cardiovascular abnormalities, including hypotension, bradycardia, QT interval prolongation, reduced adrenergic responsiveness, and a predisposition to hypovolemic shock and acute renal failure [6-9]. Cardiac dysfunction in patients with OJ is primarily characterized by reduced cardiac output, leading to decreased exercise capacity and an elevated risk of perioperative mortality [10]. The relationship between OJ and cardiac injury was first described by Green et al. in 1986 as the "Jaundiced Heart" and is now widely recognized as a clinical phenomenon [1, 11]. OJ is known to cause significant hemodynamic disturbances. In 1991, Lumlertgul et al. studied nine jaundiced patients and eight healthy volunteers, demonstrating that jaundiced patients exhibited a blunted myocardial contractile response to inotropic stimulation [12].

In recent years, researchers have proposed that heart dysfunction induced by chronic BDL models may be classified as cirrhotic cardiomyopathy, a condition often studied in mice subjected to bile duct ligation for 28 days or longer to induce liver cirrhosis [13].

This review aims to summarize the current understanding of the mechanisms underlying cardiac injury in OJ. Based on previous studies, OJ-induced cardiac damage is associated with bile acid toxicity, endotoxemia, inflammation, oxidative stress, apoptosis, and autophagy. Given the limited research in this area, further elucidation of these mechanisms is essential to developing preventive and therapeutic strategies for OJ-associated cardiac injury.

Mechanism of OJ in heart injury

Toxic effects of bile acids

Bile acids (BAs) are essential components of bile but can exert significant toxic effects when they accumulate in the bloodstream, particularly affecting the circulatory system and the heart [14]. Under normal physiological conditions, BAs are taken up through the basolateral membrane and exported via tubular efflux pumps. However, in OJ, bile flow is obstructed, leading to the accumulation of BAs in the blood and liver cells. As early as 1964, studies demonstrated that BAs inhibit adenosine triphosphatase (ATPase) activity, reduce oxygen consumption, and impair protein synthesis in the intestines of rats [15]. Some scholars have proposed that BA toxicity contributes to cardiac injury [16].

The earliest available literature indicates a study in 1909 indicated that the association between BAs and bradycardia was first described in 1863 and suggested that BAs could cause jaundice-associated bradycardia [17]. Later, in 1939 and 1940, Wakim, Essex, and Mann used a rabbit model and found that bile salts induced bradycardia, negative inotropism, and even cardiac arrest, confirming the cardiotoxic effects of BAs [18-20]. In 1983, Bogin et al. demonstrated in both in vitro and in vivo studies that BAs reduced the beating rate of cardiomyocytes in a concentration- and time-dependent manner [21].

Mitochondrial dysfunction plays a key role in BA-induced toxicity. Previous studies have confirmed that high BA concentrations impair mitochondrial structure and function [22]. When BA levels exceed the binding capacity of cytoplasmic binding proteins in hepatocytes, they induce apoptosis and necrosis by damaging mitochondria [23]. Similarly, cardiac mitochondria are highly susceptible to BA toxicity, particularly hydrophobic BAs, which exert potent harmful effects. In 1997, electron microscopy studies revealed that the myocardial mitochondria of male Sprague-Dawley rats exhibited swelling and a reduction in number 14 days after BDL. Furthermore, in rats that did not undergo BDL but received gastric intubation of sodium cholate, myocardial injury was observed when serum cholate levels reached concentrations equivalent to those in the BDL group, further confirming the toxic effects of BAs on the heart [16].

BAs impair myocardial contractile responses to positive inotropy by disrupting cardiomyocyte metabolism, membrane integrity, and ion transport mechanisms. Additionally, they interfere with calcium homeostasis by affecting the uptake and release of calcium from the sarcoplasmic reticulum, leading to reduced mitochondrial function and impaired cardiac performance in the presence of high BA concentrations [24]. An in vitro study conducted in 1987 using Sprague-Dawley rat papillary muscles and isolated ventricular myocytes evaluated myocardial contractility, action potentials, and membrane currents [25]. It was found that taurine-conju-

gated bile acids interact with muscarinic M2 receptors, reducing intracellular cyclic adenosine monophosphate levels and exerting a negative chronotropic effect on cardiomyocytes [26].

BAs have also been shown to shorten ventricular action potential duration, reduce inward ionic currents, and enhance outward potassium currents. These alterations may contribute to negative inotropic effects and abbreviated action potentials [25]. Furthermore, high BA concentrations damage cardiomyocytes by activating the G protein-coupled receptor 5 and the farnesoid X receptor. Cell-based studies have demonstrated that hydrophobic BAs, such as chenodeoxycholic acid, activate farnesoid X receptor in cardiomyocytes, promoting inflammation and apoptosis. Additionally, excessive BAs reduce fatty acid oxidation in cardiomyocytes, potentially leading to cardiac insufficiency [27, 28].

Endotoxin

Endotoxin, also known as lipopolysaccharide (LPS), is a major component of the cell wall in Gram-negative bacteria and exhibits strong immunogenicity and toxicity [29, 30]. The high incidence of postoperative complications in patients with OJ is significantly influenced by endotoxemia [31].

In an experimental rabbit model of OJ, serum total bilirubin, transaminase, and endotoxin levels were measured on days 2, 5, 8, and 13 post-surgery. The results showed that rabbits in the OJ group had a higher frequency of endotoxemia in both the portal vein and systemic circulation compared to the sham-operated group [32]. Patients with OJ are prone to endotoxemia, primarily due to increased absorption of endotoxins from the intestinal lumen and reduced clearance by the liver reticuloendothelial system [32]. In OJ, endotoxemia exacerbates organ injury through excessive endotoxin release [33].

Endotoxins contribute to vascular damage by intensifying systemic inflammation. Studies have shown that the inflammatory response, primarily driven by the activation of the nuclear factor kappa B (NF-κB) signaling pathway and the upregulation of inflammatory cytokines such as tumor necrosis factor-alpha, plays a crucial role in endotoxin-induced myocardial injury [34]. During endotoxemia, LPS interacts with toll-like receptor 4 on immune and non-immune cells, leading to toll-like receptor 4 upregulation and NF-κB pathway activation. This results in increased expression of phosphorylated NF-κB and phosphorylated I-kappa-B-alpha, which further induces the overexpression of pro-inflammatory cytokines, including interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha, ultimately leading to myocardial injury [35]. In addition, LPS not only activates NF-κB but also triggers the NOD-like receptor protein 3 inflammasome, leading to the cleavage of Gasdermin D into its active N-Gasdermin D form. This activation promotes the cleavage of caspase-1 and increases the levels of interleukin-1 beta, interleukin-18, and reactive oxygen species (ROS), ultimately inducing pyroptosis in cardiomyocytes [36].

Furthermore, endotoxins stimulate macrophages to generate reactive free radicals and release lysosomal enzymes, which contribute to myocardial cell damage [37]. LPS also induces oxidative stress, further exacerbating myocardial injury and impairing cardiac contractility. Therefore, endotoxin plays a critical role in OJ-related cardiac injury.

Oxidative stress

Oxidative stress is an imbalance between the production of ROS and the endogenous antioxidant defense mechanisms, leading to redox dysregulation [38]. Previous studies have demonstrated that OJ induces systemic oxidative stress in multiple organs, including the heart, liver, kidneys, brain, lungs, blood, and intestines [39-44]. Due to their hydrophobic nature, bile acids disrupt membrane stability and impair organelle structure and function, particularly in mitochondria. This disruption results in increased oxygen free radicals and lipid peroxidation products, thereby disturbing redox homeostasis. Additionally, toxic bile acids activate membrane-associated proteins, such as nicotinamide adenine dinucleotide phosphate oxidases, which catalyze ROS production [45]. In 2009, Cruz and Shafarood used a BDL mouse model to demonstrate significant oxidative damage in cardiac tissue, characterized by elevated levels of malondialdehyde and nicotinamide adenine dinucleotide phosphate, along with reduced activity of antioxidant enzymes such as catalase and glutathione peroxidase [46, 47].

Bile acids also induce endoplasmic reticulum oxidative stress, leading to the release of calcium ions (Ca^{2+}) into the cytoplasm. The increased intracellular Ca^{2+} concentration further stimulates mitochondria to overproduce ROS, exacerbating oxidative stress [48]. ROS can enhance Ca^{2+} influx through L-type calcium channels and reverse the function of the Na^{+}/Ca^{2+}

exchanger, causing excessive Ca^{2+} inflow and Na^{+} outflow, which severely disrupts cardiac electrophysiology. Additionally, excessive ROS inhibit sarcoplasmic reticulum calcium ATPase activity, resulting in Ca^{2+} overload, reduced calcium sensitivity of myofilaments, and ultimately impaired cardiac contractile function [49].

Cardiac myocytes are rich in mitochondria, the primary source of ROS. Under pathological conditions, toxic bile acids directly interfere with mitochondrial respiratory complexes and the electron transport chain, leading to excessive ROS production. This disrupts the balance of proteins involved in mitochondrial fusion and fission, inducing apoptosis. The ROS generated by mitochondria, known as mitochondrial ROS, damage mitochondrial DNA and lipids, impair myocardial energy metabolism, and contribute to cardiomyocyte apoptosis and heart failure [50, 51].

Moreover, ROS activate inflammatory pathways, promoting the infiltration of inflammatory cells and the release of inflammatory mediators [52]. Excessive ROS production also triggers lipid peroxidation of myocardial cell membranes, leading to structural and functional damage, culminating in apoptosis and necrosis of cardiomyocytes. In summary, these findings suggest that oxidative stress plays a crucial role in OJ-induced cardiac injury.

Inflammation

Inflammation is the body's immune defense mechanism against injury, infection, and other harmful stimuli [53]. An increasing number of studies suggest a strong association between inflammation and cardiovascular diseases, with inflammation playing a critical role in conditions such as myocardial infarction and heart failure [54]. In OJ, inflammatory injury has also been observed in cardiac tissue. In 2021, Ommati et al. reported that the most prominent lesion in the cardiac tissue of BDL rats was inflammation [55].

Excessive oxygen free radicals and other ROS can activate immune cells and trigger inflammatory pathways such as NF-κB, c-Jun N-terminal kinase, and activator protein 1, ultimately leading to an inflammatory response [56, 57]. Biliary obstruction and bile deficiency are key pathological events that compromise gut barrier integrity. When OJ patients develop gut barrier dysfunction, elevated endotoxin levels in the portal and systemic circulation trigger a systemic inflammatory response. This leads to the release of cytokines and proinflammatory mediators such as tumor necrosis factor-alpha and interleukin-6 into the bloodstream, exacerbating systemic and cardiac inflammation [58]. These findings indicate that inflammation plays a significant role in OJ-induced cardiac injury.

Nitric oxide

Nitric oxide (NO) is a potent vasodilator synthesized by vascular endothelial cells. It induces vasodilation by activating guanylate cyclase, thereby increasing intracellular cyclic guanosine monophosphate levels [59]. Excessive NO production has been implicated in cardiovascular dysfunction, including decreased vascular responsiveness to adrenergic receptor agonists and the induction of bradycardia in OJ animal models [8, 9].

In OJ, endotoxins activate vascular smooth muscle cells and macrophages, leading to excessive NO production [60]. This disrupts the balance between vasodilation and vasoconstriction, resulting in persistent vasodilation, reduced blood pressure, and impaired coronary perfusion [61]. In 2005, researchers isolated thoracic aortas from rats and mice and precontracted the vessels with phenylephrine before examining the effects of acetylcholine and taurine-conjugated deoxycholic acid in the presence or absence of a nitric oxide synthase inhibitor and lithocholic acid (a bile acid). Their findings confirmed that the vasodilatory effects of bile acids were NO- and endothelium-dependent [62].

Moreover, NO contributes to cardiomyocyte apoptosis by regulating multiple signaling pathways [63]. In BDL mice, intraperitoneal injection of L-NAME (a non-selective nitric oxide synthase inhibitor) reduced myocardial NO levels, improved cardiac structural abnormalities, and decreased cardiomyocyte apoptosis [47]. These findings suggest that NO plays a crucial role in the pathogenesis of jaundice-related cardiac injury and may exacerbate myocardial damage under pathological conditions.

Autophagy

Autophagy is a highly conserved cellular process that delivers cytosolic components to lysosomes for degradation and recycling. The term "autophagy," derived from the Greek words for "self-eating," was first introduced by Deter in 1967 [64, 65]. Autophagy plays a critical role in maintaining cardiac structure and function. Previous studies have demonstrated its involvement in various cardiac diseases, including diabetic cardiomyopathy, doxorubicin-induced

cardiomyopathy, myocardial ischemia, heart failure, and genetic cardiomyopathy [66-70]. By clearing misfolded proteins, damaged mitochondria, and other organelles, autophagy contributes to the preservation of normal cardiac function [71]. Additionally, research has suggested that autophagy plays a significant role in organ injury, including liver and intestinal damage, in OJ [72, 73].

In 2024, Wang et al. investigated myocardial injury induced by common bile duct ligation in rats. Their study showed that under OJ conditions, cardiac tissue exhibited increased levels of autophagy markers, such as light chain 3-II and Beclin-1 [74]. Furthermore, cholestasis inhibits autolysosome formation. Cholesterol 7α-hydroxylase catalyzes the conversion of cholesterol into bile acids, which subsequently activate the nuclear receptors farnesoid X receptor and intestinal fibroblast growth factor, both of which suppress autophagy-related transcriptional genes [75].

In the late stages of OJ, decreased connexin 43 expression leads to excessive autophagy activation through the adenosine monophosphate-activated protein kinase-mammalian target of rapamycin-unc-51-like autophagy activating kinase 1 signaling pathway, further exacerbating myocardial injury [74]. Additionally, bile acids upregulate p62 and Beclin-1 expression, thereby enhancing autophagy. The phosphatidylinositol 3-kinase-Beclin complex recruits the autophagy-related 12-autophagy-related 5 complex and autophagy-related 16 multimers. These proteins, along with microtubule-associated protein light chain 3, promote the formation of autophagic vesicles [76].

These findings highlight the significant role of autophagy in cardiac injury caused by OJ. However, studies investigating the involvement of autophagy in OJ-induced cardiac injury remain limited. Nevertheless, current evidence suggests that autophagy is a key mechanism underlying jaundice-associated cardiac dysfunction and warrants further investigation.

Apoptosis

Apoptosis is a key mechanism of programmed cell death. The term “apoptosis” was first introduced by Kerr et al. in 1972 to describe a distinct form of morphological cell death [77]. To date, numerous studies have demonstrated the role of apoptosis in various cardiac diseases, including myocardial infarction, heart failure, coronary artery disease, myocardial ischemia, ischemia/reperfusion injury, and diabetic cardiomyopathy [78-80]. Recent research has also indicated that OJ induces cardiomyocyte apoptosis [81]. Apoptosis is mediated through two major pathways: the intrinsic and extrinsic pathways [82]. The intrinsic pathway is triggered by factors such as ischemia, hypoxia, oxidative stress, DNA damage, and toxic drugs effects [83]. In contrast, the extrinsic pathway is typically activated by death receptor superfamily ligands, such as tumor necrosis factor-alpha [84, 85].

In 2010, BDL mouse experiments demonstrated positive TUNEL staining in myocardial tissue from cholestatic mice on day 3, indicating increased apoptosis [47]. In 2014, Abbasi et al. further confirmed an increased number of apoptotic cardiomyocytes in a rat model of bile duct ligation, supporting the role of apoptosis in the pathogenesis of the “Jaundiced Heart” [86]. That same year, Nam et al. investigated the apoptotic pathways involved in myocardial apoptosis in BDL mice after two weeks [87]. They intravenously injected CD178 [Fas ligand (FasL)] monoclonal antibodies via the caudal vein at day 12 post-BDL and found that FasL antibody treatment significantly improved myocardial contractility in BDL mice. Their study also demonstrated that the Fas receptor, a member of the TNF superfamily, recruits the adaptor protein Fas-associated death domain- and caspases upon trimerization, forming a multiprotein complex. This process leads to the recruitment of caspase-8, initiating a cascade that ultimately activates caspase-3 and caspase-7, thereby triggering the extrinsic apoptosis pathway [87].

B-cell lymphoma-2 (Bcl-2) associated X protein and Bcl-2 are key members of the Bcl-2 protein family and play crucial roles in apoptosis, particularly in the intrinsic pathway. Bcl-2 associated X protein, a pro-apoptotic protein, induces mitochondrial outer membrane permeabilization, leading to the release of pro-apoptotic factors such as cytochrome c into the cytoplasm. This, in turn, activates cytosolic signaling pathways, recruiting caspase recruitment domain proteins to caspase-9, ultimately triggering apoptosis through caspase activation and resulting in cell death [88]. In 2021, Moheimani et al. demonstrated that in BDL rats, activation of caspases, along with the involvement of Bcl-2 associated X protein and Bcl-2 family proteins, plays a central role in myocardial apoptosis [89]. These studies collectively confirm that apoptosis is a key mechanism in myocardial injury induced by BDL.

Current treatment influencing factors

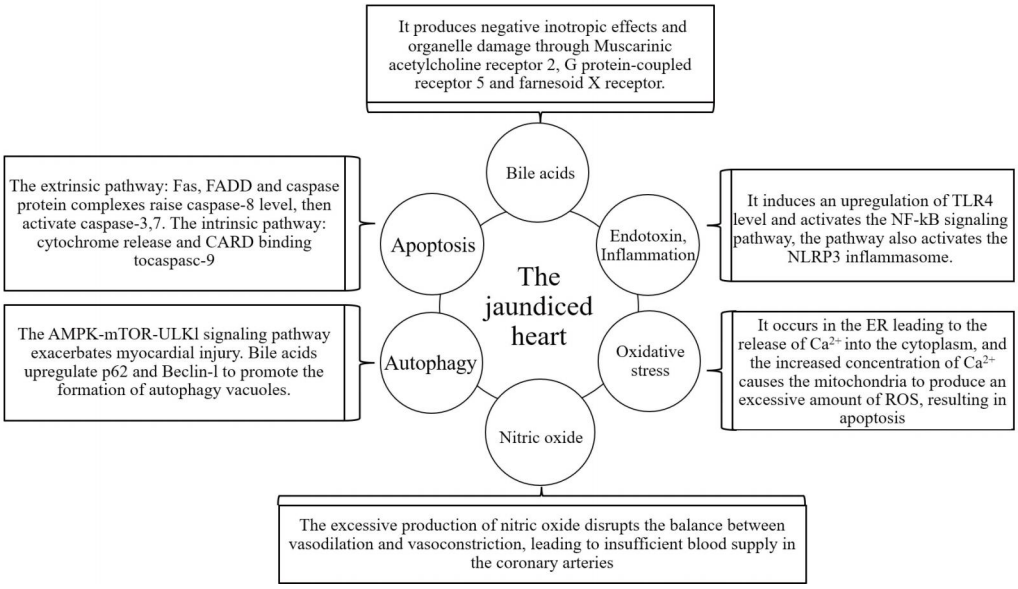


Figure 1. Illustration of the mechanisms of cardiac injury in obstructive jaundice. TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor (NLR) family pyrin domain-containing 3; ER, endoplasmic reticulum; AMPK, Adenosine monophosphate-activated protein kinase; m-TOR, mammalian target of rapamycin; ULK1, Unc-51 like autophagy activating kinase 1; Fas, Fas cell surface death receptor; FADD, Fas-associated protein with death domain.

Currently, there are no well-established preventive measures for cardiac injury in OJ. In this review, we summarize treatment-related factors that may influence the prognosis of OJ-induced cardiac injury.

Selection of anesthetic drugs

Patients with OJ undergoing anesthesia experience significant fluctuations in mean arterial pressure before and after induction, making them more susceptible to hypotension or bradycardia. Additionally, the incidence of delayed postoperative awakening in OJ patients is higher than in non-OJ patients [90]. Therefore, careful selection of anesthetic agents is crucial.

Propofol, a widely used intravenous anesthetic, has cardiovascular depressant effects. In a study using male Sprague-Dawley rats with BDL models, researchers found that myocardial function was impaired in the BDL group. Low to moderate concentrations of propofol did not further impair cardiac function, whereas high doses significantly reduced myocardial performance [91]. Thus, propofol should be administered with caution in OJ patients, with careful dose adjustment and continuous cardiac monitoring to prevent excessive myocardial suppression. Interestingly, propofol has also been found to protect vascular endothelial cells by significantly reducing H_2O_2-induced caspase-3 activity, thereby inhibiting apoptosis and exerting a cardioprotective effect [92].

Etomidate, another commonly used anesthetic, has also been studied in the context of OJ. However, its relationship with OJ-related cardiac injury remains poorly understood. Song et al. compared 20 OJ patients with 20 non-OJ patients and found that the OJ group required lower doses of etomidate than the control group [93]. These findings suggest that different anesthetic agents may have varying effects on OJ patients. Anesthetic selection should be carefully considered to avoid exacerbating cardiac injury in this population.

Traditional Chinese medicine (TCM)

TCM has shown has shown potential in preventing cardiac injury in OJ. Alam et al. proposed that the combination of lupeol and naringin effectively alleviates myocardial injury in BDL rats. This combination enhances antioxidant enzyme activity (superoxide dismutase, catalase, and Glutathione), scavenges free radicals, and reduces oxidative stress, thereby protecting cardiomyocytes. Additionally, it inhibits NF-κB/p65 expression, suppressing inflammatory responses and further preventing myocardial damage [94].

Astragalus, a well-known TCM herb, has been studied for its cardioprotective effects. Astragaloside IV, a bioactive compound found in Astragalus roots, has been shown to reduce isoproterenol-induced myocardial injury by decreasing cytoplasmic Ca^{2+} levels. Additionally, it

lowers malondialdehyde levels while increasing superoxide dismutase activity, suggesting that its antioxidant properties may contribute to its cardioprotective effects [95].

Perioperative impact

Optimizing preoperative assessment, intraoperative management, and postoperative care can improve patient prognosis and reduce mortality. Preoperative biliary drainage helps lower bilirubin levels, mitigate cardiotoxic effects, and enhance cardiovascular function. During surgery, patients with OJ are prone to hypovolemia, necessitating aggressive fluid therapy to maintain adequate circulating blood volume. Additionally, due to the high incidence of cardiovascular depression in these patients, continuous cardiovascular monitoring is essential. Cardiovascular support medications should be administered as needed to stabilize blood pressure and heart rate [96].

Future research

A 2024 study on OJ rats revealed that elevated bile acid levels, in conjunction with increased LPS concentrations, induce pyroptosis and exacerbate hepatic injury [97]. Extensive evidence has demonstrated the role of pyroptosis in various forms of myocardial injury [98]. However, few studies have investigated the role of pyroptosis in OJ-induced cardiac injury. Whether pyroptosis occurs in the myocardium of patients with OJ remains an open question, warranting further research.

Current research on cardiac injury in OJ remains limited, and many areas require further exploration. Omics technologies, with their high-throughput and high-sensitivity capabilities, enable dynamic monitoring of endogenous small-molecule metabolites. By systematically analyzing metabolic changes under physiological and pathological conditions, omics research can provide valuable insights into the complex mechanisms underlying OJ-induced cardiac injury.

Conclusion

OJ can lead to multiple systemic complications, with the heart being one of the most affected organs. The clinical manifestations of OJ-induced cardiac injury are diverse, significantly impacting patients' quality of life and prognosis. Early identification and intervention are crucial for improving patient outcomes.

The toxic effects of bile acids, inflammation, oxidative stress, endotoxemia, NO dysregulation, apoptosis, and pyroptosis all contribute to OJ-related cardiac injury. As illustrated in **Figure 1**, these mechanisms are interconnected. Bile acids and endotoxins can directly trigger inflammatory responses or exacerbate inflammation by increasing oxidative stress. Apoptosis and autophagy are often induced by bile acid toxicity, while abnormal regulation of these processes, combined with severe inflammatory responses, leads to myocardial cell damage.

This review summarizes current research on the mechanisms of cardiac injury in OJ. Furthermore, it proposes potential therapeutic strategies and research directions for future studies.

Author contributions: Chunyang Li drafted the manuscript, while Mingyao Chen and Dedong Zhang contributed to the literature collection. Zhenmeng Wang and Tianying Xu reviewed the manuscript. All authors approved the final manuscript.

References

[1] Green J, Better OS. Systemic hypotension and renal failure in obstructive jaundice-mechanistic and therapeutic aspects. J Am Soc Nephrol 1995;5(11):1853-1871.

[2] Sheen JM, Chen YC, Tain YL, et al. Increased circulatory asymmetric dimethylarginine and multiple organ failure: bile duct ligation in rat as a model. Int J Mol Sci 2014;15(3):3989-4006.

[3] Krones E, Pollheimer MJ, Rosenkranz AR, et al. Cholemic nephropathy - Historical notes and novel perspectives. Biochim Biophys Acta Mol Basis Dis 2018;1864(4 Pt B):1356-1366.

[4] Pavlidis ET, Pavlidis TE. Pathophysiological consequences of obstructive jaundice and perioperative management. Hepatobiliary Pancreat Dis Int 2018;17(1):17-21.

[5] Mariotti V, Strazzabosco M, Fabris L, et al. Animal models of biliary injury and altered bile acid metabolism. Biochim Biophys Acta Mol Basis Dis 2018;1864(4 Pt B):1254-1261.

[6] Williams RD, Elliott DW, Zollinger RM. The effect of hypotension in obstructive jaundice. Arch Surg 1960;81:334-340.

[7] Tajuddin M, Tariq M, Bilgrami NL, et al. Biochemical and pathological changes in the heart following bile duct ligation. Adv Myocardiol 1980;2:209-212.

[8] Namiranian K, Samini M, Mehr SE, et al. Mesenteric vascular bed responsiveness in bile duct-ligated rats: roles of opioid and nitric oxide systems. Eur J Pharmacol 2001;423(2-3):185-193.

[9] Mani AR, Nahavandi A, Moosavi M, et al.

Dual nitric oxide mechanisms of cholestasis-induced bradycardia in the rat. Clin Exp Pharmacol Physiol 2002;29(10):905-908.
[10] Junejo MA, Siriwardena AK, Parker MJ. Peripheral oxygen extraction in patients with malignant obstructive jaundice. Anaesthesia 2014;69(1):32-36.
[11] Green J, Beyar R, Sideman S, et al. The "jaundiced heart": a possible explanation for postoperative shock in obstructive jaundice. Surgery 1986;100(1):14-20.
[12] Lumlertgul D, Boonyaprapa S, Bunnachak D, et al. The jaundiced heart: evidence of blunted response to positive inotropic stimulation. Ren Fail 1991;13(1):15-22.
[13] Uhlig M, Hein M, Habigt MA, et al. Cirrhotic Cardiomyopathy Following Bile Duct Ligation in Rats-A Matter of Time? Int J Mol Sci 2023;24(9):8147.
[14] Zhang Z, Lv T, Wang X, et al. Role of the microbiota-gut-heart axis between bile acids and cardiovascular disease. Biomed Pharmacother 2024;174:116567.
[15] Parkinson TM, Olson JA. INHIBITORY EFFECTS OF BILE ACIDS ON ADENOSINE TRIPHOSPHATASE, OXYGEN CONSUMPTION, AND THE TRANSPORT AND DIFFUSION OF WATER-SOLUBLE SUBSTANCES IN THE SMALL INTESTINE OF THE RAT. Life Sci (1962) 1964;3:107-112.
[16] Mu YP, Peng SY. Relation between bile acids and myocardial damage in obstructive jaundice. World J Gastroenterol 1997;3(3):174-176.
[17] King JH, Stewart HA. EFFECT OF THE INJECTION OF BILE ON THE CIRCULATION. J Exp Med 1909;11(5):673-685.
[18] Joubert P. Cholic acid and the heart: in vitro studies of the effect on heart rate and myocardial contractility in the rat. Clin Exp Pharmacol Physiol 1978;5(1):9-16.
[19] Wakim KG, Essex. Mann FC. The effects of whole bile and bile salts on the perfused heart. Am Heart J 1939;171-175.
[20] Wakim KG, Essex. Mann FC. The effects of whole bile and bile salts on the innervated and the denervated heart. Am Heart J 1940;486-491.
[21] Bogin E, Better O, Harari I. The effect of jaundiced sera and bile salts on cultured beating rat heart cells. Experientia 1983;39(11):1307-1308.
[22] Spivey JR, Bronk SF, Gores GJ. Glycochenodeoxycholate-induced lethal hepatocellular injury in rat hepatocytes. Role of ATP depletion and cytosolic free calcium. J Clin Invest 1993;92(1):17-24.
[23] Palmeira CM, Rolo AP. Mitochondrially-mediated toxicity of bile acids. Toxicology 2004;203(1-3):1-15.
[24] Ferreira M, Coxito PM, Sardão VA, et al. Bile acids are toxic for isolated cardiac mitochondria: a possible cause for hepatic-derived cardiomyopathies? Cardiovasc Toxicol 2005;5(1):63-73.
[25] Binah O, Rubinstein I, Bomzon A, et al. Effects of bile acids on ventricular muscle contraction and electrophysiological properties: studies in rat papillary muscle and isolated ventricular myocytes. Naunyn Schmiedebergs Arch Pharmacol 1987;335(2):160-165.
[26] Sheikh Abdul Kadir SH, Miragoli M, Abu-Hayyeh S, et al. Bile acid-induced arrhythmia is mediated by muscarinic M2 receptors in neonatal rat cardiomyocytes. PLoS One 2010;5(3):e9689.
[27] Vasavan T, Ferraro E, Ibrahim E, et al. Heart and bile acids - Clinical consequences of altered bile acid metabolism. Biochim Biophys Acta Mol Basis Dis 2018;1864(4 Pt B):1345-1355.
[28] Jia W, Li Y, Cheung KCP, et al. Bile acid signaling in the regulation of whole body metabolic and immunological homeostasis. Sci China Life Sci 2024;67(5):865-878.
[29] Foster DM, Kellum JA. Endotoxic Septic Shock: Diagnosis and Treatment. Int J Mol Sci 2023;24(22):16185.
[30] Nguyen M, Gautier T, Masson D, et al. Endotoxemia in Acute Heart Failure and Cardiogenic Shock: Evidence, Mechanisms and Therapeutic Options. J Clin Med 2023;12(7):2579.
[31] Yorganci K, Baykal A, Kologlu M, et al. Endotoxin challenge causes a proinflammatory state in obstructive jaundice. J Invest Surg 2004;17(3):119-126.
[32] Papakostas C, Bezirtzoglou E, Pitiakoudis M, et al. Endotoxinemia in the portal and the systemic circulation in obstructive jaundice. Clin Exp Med 2003;3(2):124-128.
[33] Song JG, Cao YF, Sun YM, et al. Baroreflex sensitivity is impaired in patients with obstructive jaundice. Anesthesiology 2009;111(3):561-565.
[34] Tang F, Liu D, Wan F, et al. Ameliorative effect of anisodamine (654-1/654-2) against myocardial dysfunction induced by septic shock via the NF-κB/NLRP-3 or the PI3K-AKT/NF-κB pathway. Phytomedicine 2024;123:155277.
[35] Wang SM, Liu GQ, Xian HB, et al. LncRNA NEAT1 alleviates sepsis-induced myocardial injury by regulating the TLR2/NF-κB signaling pathway. Eur Rev Med Pharmacol Sci 2019;23(11):4898-4907.
[36] El-Sisi AEE, Sokar SS, Shebl AM, et al. Octreotide and melatonin alleviate inflammasome-induced pyroptosis through inhibition of TLR4-NF-κB-NLRP3 pathway in

hepatic ischemia/reperfusion injury. Toxicol Appl Pharmacol 2021;410:115340.
[37] Scott-Conner CE, Grogan JB. Serum and cellular factors in murine obstructive jaundice. Surgery 1994;115(1):77-84.
[38] Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol 2011;301(6):H2181-2190.
[39] Tsai LY, Lee KT, Liu TZ. Evidence for accelerated generation of hydroxyl radicals in experimental obstructive jaundice of rats. Free Radic Biol Med 1998;24(5):732-737.
[40] Assimakopoulos SF, Vagianos CE, Patsoukis N, et al. Evidence for intestinal oxidative stress in obstructive jaundice-induced gut barrier dysfunction in rats. Acta Physiol Scand 2004;180(2):177-185.
[41] Assimakopoulos SF, Vagianos CE, Zervoudakis G, et al. Gut regulatory peptides bombesin and neurotensin reduce hepatic oxidative stress and histological alterations in bile duct ligated rats. Regul Pept 2004;120(1-3):185-193.
[42] Ara C, Karabulut AB, Kirimlioglu H, et al. Protective effect of resveratrol against renal oxidative stress in cholestasis. Ren Fail 2005;27(4):435-440.
[43] Chroni E, Patsoukis N, Karageorgos N, et al. Brain oxidative stress induced by obstructive jaundice in rats. J Neuropathol Exp Neurol 2006;65(2):193-198.
[44] Tieppo J, Vercelino R, Dias AS, et al. Evaluation of the protective effects of quercetin in the hepatopulmonary syndrome. Food Chem Toxicol 2007;45(7):1140-1146.
[45] Orozco-Aguilar J, Simon F, Cabello-Verrugio C. Redox-Dependent Effects in the Physiopathological Role of Bile Acids. Oxid Med Cell Longev 2021;2021:4847941.
[46] Cruz A, Tasset I, Ramírez LM, et al. Effect of melatonin on myocardial oxidative stress induced by experimental obstructive jaundice. Rev Esp Enferm Dig 2009;101(7):460-463.
[47] Shafaroodi H, Ebrahimi F, Moezi L, et al. Cholestasis induces apoptosis in mice cardiac cells: the possible role of nitric oxide and oxidative stress. Liver Int 2010;30(6):898-905.
[48] Che Y, Xu W, Ding C, et al. Bile acids target mitofusin 2 to differentially regulate innate immunity in physiological versus cholestatic conditions. Cell Rep 2023;42(1):112011.
[49] van der Pol A, van Gilst WH, Voors AA, et al. Treating oxidative stress in heart failure: past, present and future. Eur J Heart Fail 2019;21(4):425-435.
[50] Goicoechea L, Conde de la Rosa L, Torres S, et al. Mitochondrial cholesterol: Metabolism and impact on redox biology and disease. Redox Biol 2023;61:102643.
[51] Viola HM, Hool LC. Targeting calcium and the mitochondria in prevention of pathology in the heart. Curr Drug Targets 2011;12(5):748-760.
[52] Kim JA, Montagnani M, Koh KK, et al. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113(15):1888-1904.
[53] Duodu P, Sosa G, Canar J, et al. Exposing the Two Contrasting Faces of STAT2 in Inflammation. J Interferon Cytokine Res 2022;42(9):467-481.
[54] Suetomi T, Miyamoto S, Brown JH. Inflammation in nonischemic heart disease: initiation by cardiomyocyte CaMKII and NLRP3 inflammasome signaling. Am J Physiol Heart Circ Physiol 2019;317(5):H877-H890.
[55] Ommati MM, Amjadinia A, Mousavi K, et al. N-acetyl cysteine treatment mitigates biomarkers of oxidative stress in different tissues of bile duct ligated rats. Stress 2021;24(2):213-228.
[56] Sul OJ, Ra SW. Quercetin Prevents LPS-Induced Oxidative Stress and Inflammation by Modulating NOX2/ROS/NF-kB in Lung Epithelial Cells. Molecules 2021;26(22):6949.
[57] Yin X, Zhuang X, Luo W, et al. Andrographolide promote the growth and immunity of Litopenaeus vannamei, and protects shrimps against Vibrio alginolyticus by regulating inflammation and apoptosis via a ROS-JNK dependent pathway. Front Immunol 2022;13:990297.
[58] Assimakopoulos SF, Scopa CD, Vagianos CE. Pathophysiology of increased intestinal permeability in obstructive jaundice. World J Gastroenterol 2007;13(48):6458-6464.
[59] Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991;337(8744):776-778.
[60] Jolobe OM. Role of endotoxin and nitric oxide in the pathogenesis of renal failure in obstructive jaundice. Br J Surg 1997;84(12):1747.
[61] Gray GA, Schott C, Julou-Schaeffer G, et al. The effect of inhibitors of the L-arginine/nitric oxide pathway on endotoxin-induced loss of vascular responsiveness in anaesthetized rats. Br J Pharmacol 1991;103(1):1218-1224.
[62] Khurana S, Yamada M, Wess J, et al. Deoxycholyltaurine-induced vasodilation of rodent aorta is nitric oxide- and muscarinic M(3) receptor-dependent. Eur J Pharmacol 2005;517(1-2):103-110.
[63] Razavi HM, Hamilton JA, Feng Q. Modulation of apoptosis by nitric oxide: implications in myocardial ischemia and heart failure. Pharmacol Ther 2005;106(2):147-162.

[64] Ohsumi Y. Historical landmarks of autophagy research. Cell Res 2014;24(1):9-23.
[65] Deter RL, De Duve C. Influence of glucagon, an inducer of cellular autophagy, on some physical properties of rat liver lysosomes. J Cell Biol 1967;33(2):437-449.
[66] Chen Y, Shi S, Dai Y. Research progress of therapeutic drugs for doxorubicin-induced cardiomyopathy. Biomed Pharmacother 2022;156:113903.
[67] Dewanjee S, Vallamkondu J, Kalra RS, et al. Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. Ageing Res Rev 2021;68:101338.
[68] Ding X, Zhu C, Wang W, et al. SIRT1 is a regulator of autophagy: Implications for the progression and treatment of myocardial ischemia-reperfusion. Pharmacol Res 2024;199:106957.
[69] Li A, Gao M, Liu B, et al. Mitochondrial autophagy: molecular mechanisms and implications for cardiovascular disease. Cell Death Dis 2022;13(5):444.
[70] Choi JC, Muchir A, Wu W, et al. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation. Sci Transl Med 2012;4(144):144ra102.
[71] Sciarretta S, Maejima Y, Zablocki D, et al. The Role of Autophagy in the Heart. Annu Rev Physiol 2018;80:1-26.
[72] Zhang X, Zhang F, Zhang C, et al. miRNA-125b Signaling Ameliorates Liver Injury Against Obstructive Jaundice-Induced Excessive Fibrosis in Experimental Rats. Yonsei Med J 2021;62(5):453-460.
[73] Zhang X, Peng B, Zhang Y, et al. Biliary Drainage Reduces Intestinal Barrier Damage in Obstructive Jaundice by Regulating Autophagy. Contrast Media Mol Imaging 2022;2022:3301330.
[74] Wang X, Liao P, Dong H, et al. Reduced Cx43 Expression Induces Autophagy through Activation of the Ampk-Mtor-Ulk1 Signaling Pathway in the Common Bile Duct Ligation Rat Heart. Shock 2024;62(3):386-397.
[75] Rochette L, Dogon G, Rigal E, et al. Lipid Peroxidation and Iron Metabolism: Two Corner Stones in the Homeostasis Control of Ferroptosis. Int J Mol Sci 2022;24(1):449.
[76] Kang R, Zeh HJ, Lotze MT, et al. The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ 2011;18(4):571-580.
[77] Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972;26(4):239-257.
[78] Ouyang C, You J, Xie Z. The interplay between autophagy and apoptosis in the diabetic heart. J Mol Cell Cardiol 2014;71:71-80.
[79] Jose Corbalan J, Vatner DE, Vatner SF. Myocardial apoptosis in heart disease: does the emperor have clothes? Basic Res Cardiol 2016;111(3):31.
[80] Dong Y, Chen H, Gao J, et al. Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. J Mol Cell Cardiol 2019;136:27-41.
[81] Zhao N, Shao Z, Xia G, et al. Protective role of the CD73-A2AR axis in cirrhotic cardiomyopathy through negative feedback regulation of the NF-κB pathway. Front Immunol 2024;15:1428551.
[82] Lossi L. The concept of intrinsic versus extrinsic apoptosis. Biochem J 2022;479(3):357-384.
[83] Danial NN, Korsmeyer SJ. Cell death: critical control points. Cell 2004;116(2):205-219.
[84] Kalkavan H, Green DR. MOMP, cell suicide as a BCL-2 family business. Cell Death Differ 2018;25(1):46-55.
[85] Liu X, Kim CN, Yang J, et al. Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. Cell 1996;86(1):147-157.
[86] Abbasi A, Joharimoqaddam A, Faramarzi N, et al. Opioid receptors blockade modulates apoptosis in a rat model of cirrhotic cardiomyopathy. Ann Med Health Sci Res 2014;4(3):404-409.
[87] Nam SW, Liu H, Wong JZ, et al. Cardiomyocyte apoptosis contributes to pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated mice. Clin Sci (Lond) 2014;127(8):519-526.
[88] Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol 2020;21(2):85-100.
[89] Moheimani HR, Amiriani T, Alizadeh AM, et al. Preconditioning and anti-apoptotic effects of Metformin and Cyclosporine-A in an isolated bile duct-ligated rat heart. Eur J Pharmacol 2021;893:73807.
[90] Yang LQ, Song JC, Irwin MG, et al. A clinical prospective comparison of anesthetics sensitivity and hemodynamic effect among patients with or without obstructive jaundice. Acta Anaesthesiol Scand 2010;54(7):871-877.
[91] Ren HM, Yang LQ, Liu ZQ, et al. In vivo and ex vivo effects of propofol on myocardial performance in rats with obstructive jaundice. BMC Gastroenterol 2011;11:144.
[92] Wang B, Luo T, Chen D, et al. Propofol reduces apoptosis and up-regulates endothelial nitric oxide synthase protein expression in hydrogen peroxide-stimulated human umbilical vein endothelial cells. Anesth Analg 2007;105(4):1027-1033, table of contents.
[93] Song JC, Sun YM, Zhang MZ, et al. The etomidate requirement is decreased in

patients with obstructive jaundice. Anesth Analg 2011;113(5):1028-1032.

[94] Alam F, Kharya AK, Srivastav RK, et al. Synergetic Effect of Lupeol and Naringin Against Bile Duct Ligation Induced Cardiac Injury in Rats via Modulating Nitrite Level (eNos) and NF-kB /p65 Expression. Drug Res (Stuttg) 2023;73(1):23-29.

[95] Shahzad M, Shabbir A, Wojcikowski K, et al. The Antioxidant Effects of Radix Astragali (Astragalus membranaceus and Related Species) in Protecting Tissues from Injury and Disease. Curr Drug Targets 2016;17(12):1331-1340.

[96] Wang L, Yu WF. Obstructive jaundice and perioperative management. Acta Anaesthesiol Taiwan 2014;52(1):22-29.

[97] Shen X, Zhang X, Li K, et al. Combined bacterial translocation and cholestasis aggravates liver injury by activation pyroptosis in obstructive jaundice. Heliyon 2024;10(16):e35793.

[98] Toldo S, Mauro AG, Cutter Z, et al. Inflammasome, pyroptosis, and cytokines in myocardial ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2018;315(6):H1553-H1568.