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MITOCHONDRIAL DYSFUNCTION AND MOLECULAR BIOMARKERS IN SEPSIS-INDUCED ACUTE RESPIRATORY DISTRESS SYNDROME: GENETIC AND METABOLIC MECHANISMS

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ABSTRACT

Background: Sepsis-induced acute respiratory distress syndrome (ARDS) remains a leading cause of mortality in intensive care units due to the progression of multiple organ dysfunction. Mitochondrial dysfunction has emerged as a central mechanism contributing to the pathogenesis of critical illness, including impaired oxidative phosphorylation, excessive production of reactive oxygen species, and mitochondrial DNA damage, all of which lead to cellular energy failure and dysregulated systemic inflammation.

Objective: This study aimed to summarize current knowledge on mitochondrial dysfunction in sepsis and ARDS, and to evaluate the diagnostic and prognostic value of emerging mitochondria-associated molecular biomarkers, as well as their potential clinical applications in anesthesiology and critical care.

Materials and Methods: A comprehensive literature review was conducted using national and international databases. A total of 65 relevant publications were included, encompassing clinical, experimental, and molecular-genetic studies focused on mitochondrial pathophysiology, biomarkers of mitochondrial injury, and metabolic therapeutic approaches. Additionally, studies utilizing bioinformatics, machine learning, and single-cell transcriptomic analyses were analyzed.

Results: The analysis demonstrated that mitochondrial dysfunction represents an independent driver of multiple organ failure. Several candidate biomarkers, including ARID4B, RGS2, and TGM2, were identified as indicators of mitochondrial dysregulation in sepsis-induced ARDS. Mitochondrial alterations were strongly associated with immune imbalance and disease severity. Furthermore, biomarkers such as lactate, circulating mitochondrial DNA, cytochrome c, and oxidative stress markers showed potential for integration into risk stratification models.

Conclusion: Mitochondrial dysfunction plays a key pathogenic role in critical illness and represents a promising therapeutic target. Incorporation of mitochondria-related molecular biomarkers into clinical algorithms may improve prognostic accuracy, guide therapeutic decision-making, and enhance the effectiveness of personalized intensive care strategies in patients with severe sepsis and ARDS.

KEYWORDS: mitochondrial dysfunction, sepsis, acute respiratory distress syndrome, mitochondrial DNA, molecular biomarkers, multiple organ failure, oxidative stress, intensive care.

INTRODUCTION

Mitochondrial dysfunction in critical conditions is currently considered as one of the key links in the pathogenesis of multiple organ failure, but its role in anesthesiology and intensive care is still poorly understood, especially in the context of new biomarkers and therapeutic approaches (Starostin, et al., 2023). Acute respiratory distress syndrome (ARDS), which often develops against the background of sepsis, remains a serious complication of intensive care, with a mortality rate of 35-45% worldwide, and in Russian intensive care units (Kuzheleva et al., 2025), according to observational registers, it is comparable and ranges from 30-50% depending on the severity of the condition and the availability of high-tech care (Liu et al., 2025).

In the clinical practice of an intensive care physician, the assessment of the severity of a patient's condition is traditionally based on integral scales (SOFA, APACHE II), but they do not reflect the depth of intracellular bioenergetic disorders (Khaliullin et al., 2026). In this context, the search for objective markers of mitochondrial dysfunction is of particular importance, as it allows us to supplement the macrophysiological assessment with parameters of cellular metabolism.

Despite the improvement of ventilation strategies and sedation protocols, up to 10% of patients in intensive care units and almost a quarter of patients on mechanical ventilation face the development of ARDS, which underlines the continuing severity of the problem in both global and Russian clinical practice (Ponasenko et al., 2021). Modern studies show that mitochondria are not only involved in the pathogenesis of sepsis-induced ARDS (Filev et al., 2020), but also form its metabolic and immune basis, determining the depth of cellular energy deficiency and the severity of the inflammatory response (McClintock et al., 2022). In the context of studying mitochondrial dysfunction as a key link in critical conditions, special attention is paid to the search for new biomarkers and the analysis of gene expression associated with

mitochondrial function, with a view to their subsequent integration into diagnostic and therapeutic algorithms of anesthesiology and intensive care (Lazarev et al., 2018).
However, even with the expansion of molecular understanding of mitochondrial dysfunction, its place in clinical algorithms for diagnosis, monitoring, and therapy of critical conditions, including sepsis-induced ARDS, remains poorly defined (He et al., 2026). In conditions of continuing high mortality and limited integration of mitochondrial-associated biomarkers into intensive care practice, it becomes obvious that there is a need to systematize data on new molecular markers and therapeutic strategies capable of influencing cellular bioenergetics (Huang et al., 2025). This is what determines the relevance of this review, aimed at analyzing the role of mitochondrial dysfunction as a pathogenetic mechanism of critical conditions and assessing the prospects for its targeted correction in anesthesiology and intensive care (Tan et al., 2024).
The purpose of the review is to summarize current data on the pathophysiological mechanisms of mitochondrial dysfunction in critical conditions, its role in the development of sepsis and acute respiratory distress syndrome, as well as to analyze new molecular biomarkers and therapeutic approaches in anesthesiology and intensive care with an emphasis on their diagnostic, prognostic and clinical potential in intensive care.

Historical development of ideas about the role of mitochondria in critical conditions

The first ideas about the pathogenesis of critical conditions were based on the concept of tissue hypoxia, in which the leading mechanism of multiple organ dysfunction was considered to be a decrease in oxygen delivery to tissues (Gurskaya et al., 2024). It was assumed that the restoration of systemic hemodynamics would automatically lead to normalization of cellular metabolism. However, clinical observations have shown that even with adequate perfusion, signs of organ failure may persist, which has called into question the universality of the hypoxic theory.
In the 1990s and 2000s, data accumulated on a decrease in the activity of respiratory chain complexes, a decrease in the synthesis of adenosine triphosphate (ATP), and increased production of reactive oxygen species in sepsis, shock, and other critical conditions (Wu et al., 2023). Structural changes in mitochondria, damage to mitochondrial DNA, and disruption of membrane potential have been shown to correlate with the severity of organ dysfunction. These observations contributed to the formation of the idea of mitochondrial insufficiency as an independent pathogenetic mechanism (Dutra Silva et al., 2021), and not just a secondary consequence of hypoxia (Liu et al., 2025), and laid the foundation for the concept of cytopathic hypoxia (Luo et al., 2025).
Subsequently, mitochondria began to be considered as the central link in the regulation of cellular survival, since it is at their level that the coupling of oxygen consumption and energy synthesis is realized (Zhang et al., 2025). Impaired oxidative phosphorylation, excessive generation of reactive oxygen species, and release of mitochondrial components into the extracellular space have been interpreted as key mechanisms of systemic damage in sepsis and other critical conditions. Thus, the focus of research has shifted from macrohemodynamics to intracellular bioenergetic processes.
The concept of mitochondrial dynamics was further developed - the processes of biogenesis, division, fusion, and mitophagy, on which the restoration of the cell's energy potential depends (Kraus et al., 2024). It turned out that in the unfavorable course of the critical condition, compensatory activation of biogenesis is insufficient, which leads to the progression of energy deficiency and activation of apoptosis. As a result, mitochondria have come to be seen as an integration node linking inflammation, metabolic disorders, and cell death.
The contribution of Russian researchers to the development of this paradigm is reflected in the works of D.O. Starostin, M.I. Shkerdina, A.N. Kuzovlev and A.V. Grechko (Starostin et al., 2023), which emphasizes the importance of molecular biomarkers in predicting the outcomes of critical conditions. The authors showed that circulating nucleic acids, including mitochondrial DNA, can serve as an indicator of the depth of cellular destruction and the severity of hypoxic-ischemic damage. In the study by V.I. Gurskaya et al. (Gurskaya et al., 2024) demonstrated that the levels of nuclear and mitochondrial DNA in blood plasma react sensitively to anesthetic effects, which confirms the lability of the mitochondrial genome under surgical stress. These data expand the understanding of mtDNA as a marker of systemic inflammation and tissue damage.
Foreign authors also emphasize the diagnostic and pathogenetic significance of mitochondrial parameters. In the work of He Y. and co-authors. (He et al., 2026) demonstrated that mitochondrial-associated biomarkers can be used for early diagnosis of ARDS in sepsis and risk stratification. Long G. and co-authors. (Long et al., 2022) consider the released mtDNA as an active mediator of acute lung injury, capable of enhancing the inflammatory response through activation of TLR9 and the inflammasome. Thus, mitochondrial dysfunction in sepsis goes beyond the local energy deficit and acquires systemic pathogenetic significance.
Thus, the evolution of views - from the concept of tissue hypoperfusion to the understanding of mitochondrial insufficiency as a key link in multiple organ dysfunction - reflects the transition to a deeper molecular interpretation of critical conditions (Luo et al., 2025). The integration of clinical observations and basic research makes it possible to consider mitochondrial markers not only as indicators of the severity of the condition, but also as potential therapeutic targets in anesthesiology and intensive care.

Pathophysiology of mitochondrial dysfunction in sepsis, shock, and postoperative complications

The mitochondria is a two-membrane organelle of a eukaryotic cell that has preserved its own DNA and elements of bacterial origin, which determines its special sensitivity to inflammatory and hypoxic effects. In conditions of sepsis, shock, and severe postoperative stress, it is the mitochondria that become the central target of damage, since they ensure the coupling of oxygen consumption and ATP synthesis through the oxidative phosphorylation system (Woods et al., 2021).

Oxidative phosphorylation occurs within the inner membrane of the mitochondria, where complexes I–V of the respiratory chain are localized; disruption of these complexes leads to the separation of electron transfer and ATP synthesis. In critical condition, there is a decrease in the activity of complexes I, III, and IV, which is accompanied by a decrease in membrane potential and a decrease in energy production. These changes lead to the so-called cytopathic hypoxia (Kotani et al., 2023), when oxygen delivery may be sufficient (Liang et al., 2021), but its utilization at the mitochondrial level is disrupted (Liu et al., 2022). Clinically, this is manifested by a paradoxical situation in which normalization of hemodynamic parameters is not accompanied by restoration of organ function, which confirms the need to evaluate not only systemic perfusion, but also the mitochondrial efficiency of oxygen utilization.

At the same time, the formation of reactive oxygen species increases, which occurs when oxygen is not fully restored in the respiratory chain. Excess ROS (reactive oxygen species) damage membrane lipids, proteins of ETC complexes (electron transport chain, or mitochondrial respiratory chain) and mitochondrial DNA, forming a vicious circle: damage to the respiratory chain increases electron leakage, which further increases oxidative stress. Mitochondrial DNA (mtDNA), devoid of histone protection, is particularly vulnerable to oxidative damage, which further reduces the synthesis of respiratory chain proteins and deepens energy deficiency (Dutra Silva et al., 2021).

Clinical observations have shown that the severity of mitochondrial dysfunction correlates with the severity of multiple organ failure. So, Ponasenko A.V. et al. (Dutra Silva et al., 2021) demonstrated that an increase in the level of circulating mitochondrial DNA in cardiac surgery patients is associated with the risk of developing multiple organ failure, reflecting the degree of mitochondrial damage. These data confirm that mtDNA release is not only a consequence of organelle destruction, but also a marker of the depth of systemic inflammation.

In the postoperative period, anesthetic and surgical factors additionally affect mitochondrial metabolism. Khaliullin D.M. et al. (Khaliullin et al., 2026), analyzing the features of anesthesiological management of patients with impaired energy metabolism, emphasize that even short-term metabolic overloads can increase mitochondrial instability. Foreign studies also demonstrate the association of anesthetics with changes in the expression of genes associated with mitochondrial function, as shown by Zhang Y. and co-authors. (Zhang et al., 2025) in patients after coronary artery bypass grafting.

A significant role in the pathogenesis is played by a violation of calcium homeostasis. The overload of mitochondria with calcium under conditions of ischemia-reperfusion contributes to the opening of the pore of transient permeability, loss of membrane potential and release of cytochrome c into the cytosol, which triggers apoptotic cascades. This mechanism links bioenergetic collapse with activation of programmed cell death and progression of organ dysfunction (Kotani et al., 2023).

An additional contribution is made by changes in mitochondrial dynamics - the processes of division, fusion and mitophagy. In conditions of systemic inflammation, compensatory activation of biogenesis is often insufficient (Liang et al., 2021), which leads to the accumulation of functionally defective organelles (Liu et al., 2022). Disruption of the processes of disposal of damaged mitochondria enhances ROS production and supports the inflammatory response (Shi et al., 2021).

In the lungs with ARDS and septic lesions, a decrease in the respiratory activity of the mitochondria of alveolar cells has been shown; Dutra Silva J. et al. (Dutra Silva et al., 2021) demonstrated that the restoration of mitochondrial function with the help of extracellular vesicles of mesenchymal cells improves barrier function. Kraus R.F. et al. (Kraus et al., 2024) note that mitochondrial dysfunction in neutrophils alters their phenotype and increases damaging inflammation, which highlights the connection between mitochondrial metabolism and immune dysregulation.

It should be noted that in sepsis, shock, and postoperative complications, mitochondrial dysfunction is formed due to a combined violation of oxidative phosphorylation, excessive generation of reactive oxygen species, damage to components of the respiratory chain, and depletion of energy reserves. These processes underlie the energy deficiency of the cell and create a pathophysiological platform for the development of multiple organ failure in critical condition.

Mitochondrial dysfunction as a factor of multiple organ failure

In critical condition conditions, a key link in the progression of multiple organ failure is a violation of mitochondrial respiration, leading to a decrease in ATP synthesis and the formation of cellular energy deficiency. Even with restored macro- and microcirculation, cells can remain functionally unstable due to the so-called "cytopathic hypoxia", when oxygen is present but not effectively used (Song et al., 2022). It is this energy collapse that explains the discrepancy between the relatively preserved histological picture of organs and pronounced clinical dysfunction in intensive care practice.

In the myocardium (Deng et al., 2022), a decrease in the activity of complexes I and IV of the respiratory chain is accompanied by a decrease in contractility and the formation of septic cardiomyopathy (Raupach et al., 2021), while the severity of mitochondrial respiration suppression correlates with the outcomes of the disease (Sun et al., 2023). Excessive production of nitric oxide and peroxynitrite additionally inhibits cytochrome c oxidase, increasing the decrease in oxidative phosphorylation. In the kidneys, ATP deficiency disrupts the work of Na^+/K^+-ATPase and tubular transport, which is clinically manifested by acute renal failure with minimal signs of necrosis. Similar mechanisms underlie the phenomenon of "functional" acute kidney injury, when metabolic inhibition precedes structural destruction (Lin et al., 2023). Thus, multiple organ failure can be considered as a clinical reflection of systemic energy collapse, in which mitochondrial dysfunction precedes structural tissue damage and forms the so-called "metabolic phase" of organ failure.

In the central nervous system, energy deficiency is accompanied by an imbalance of calcium homeostasis and increased oxidative stress, which contributes to the development of critical encephalopathy. In the lungs, mitochondrial dysfunction of epithelial and endothelial cells exacerbates damage to the alveolar-capillary barrier and supports the formation of acute respiratory distress syndrome (Liu et al., 2022). Thus, cardiac, renal, cerebral and respiratory insufficiency are combined by a common pathogenetic mechanism - a violation of cell bioenergetics.

Experimental data confirm that hyperlactatemia in shock can be combined with normal or even elevated tissue PO_2 levels, which indicates a defect in oxygen utilization at the mitochondrial level (Zhu et al., 2022). Clinical studies demonstrate that in non-surviving patients, the activity of mitochondrial complexes and the content of ATP are lower than in survivors, which emphasizes the prognostic significance of bioenergetic parameters. Liang C. et al., contributed to the understanding of neurotoxic mechanisms. showing the role of PINK1-dependent pathways in disrupting the mitochondrial integrity of neurons under anesthetic treatment. Shi J. et al. (Liang et al., 2021) demonstrated that preservation of mitochondrial dynamics through HIF-1a/HO-1 signaling pathways reduces the severity of acute pulmonary injury. In the future, Song K. and co-authors. (Song et al., 2022) confirmed the importance of regulating the processes of mitochondrial division and fusion in protecting lung tissue from endotoxic damage.

The totality of these data allows us to consider mitochondrial dysfunction not as a secondary consequence of hypoperfusion, but as an independent factor determining the development of multiple organ failure. Maintaining mitochondrial homeostasis and restoring bioenergetic function is a promising area in intensive care that can affect the outcomes of patients with severe critical conditions (Badwe et al., 2023). Understanding the role of mitochondria as the central link in cellular adaptation to critical stress naturally shifts the focus of research towards the search for objective markers of their damage and functional failure. In this regard, the development and implementation of modern biomarkers of mitochondrial damage, capable of reflecting the depth of bioenergetic disorders in intensive care practice, is of particular relevance.

Modern biomarkers of mitochondrial damage in intensive care

In recent years, intensive care has become increasingly interested in finding biomarkers that reflect not only systemic inflammation, but also deep-seated disorders of cellular bioenergetics, primarily mitochondrial dysfunction. Lactate remains one of the most widely used indicators, but its increase in sepsis and shock is now considered not only as a sign of tissue hypoxia, but also as a reflection of stress-induced increased aerobic glycolysis and metabolic restructuring of the cell (Khaliullin et al., 2026). Modern concepts suggest that hyperlactatemia can perform an adaptive function, ensuring the redistribution of energy substrates (Huang et al., 2025) and the maintenance of oxidative processes under conditions of systemic stress, which requires careful interpretation of this indicator in clinical practice (Liu et al., 2022).

At the same time, the assessment of circulating mitochondrial DNA as a marker of cellular damage and activation of danger mechanisms is becoming increasingly important. The contribution of Russian researchers is reflected in the work of Khaliullin D.M., Lazarev V.V., Gilfanov A.M. (Khaliullin et al., 2026), which emphasizes the role of mitochondrial components in the formation of a systemic inflammatory response under anesthetic treatment. Filev A.D. and Pisarev V.M. (Filev et al., 2020) showed that extracellular DNA, including mtDNA, can be considered as an early indicator of the severity of urgent conditions and the depth of cellular destruction. An increase in the level of mtDNA in blood plasma is associated with the development of multiple organ failure and correlates with the SOFA score, which is confirmed by clinical observations in cardiac surgery patients (Li et al., 2023).

Special attention is paid to cytochrome c as a protein of the respiratory chain, the release of which into the systemic circulation reflects damage to mitochondrial membranes and activation of apoptosis. In clinical studies in patients with ischemic heart failure, it has been shown that higher concentrations of cytochrome c are associated with a decrease in the left ventricular ejection fraction and a deterioration in exercise tolerance (Lazarev et al., 2018). These observations allow us to consider cytochrome c as a potential marker of the severity of mitochondrial dysfunction and the functional status of a patient in the intensive care unit.

Indicators of oxidative stress, including reactive oxygen species and lipid peroxidation products, are of additional interest, since oxidative damage is one of the key mechanisms for disrupting the structure of mtDNA and enzyme complexes of the respiratory chain. Research by Zhang S. et al. (Zhang et al., 2024) demonstrate the possibility of metabolomic analysis as a tool for early stratification of patients with respiratory dysfunction, whereas Song K. et al. (Song et al., 2022) and Deng X. et al. (Deng et al., 2022) have shown that pharmacological modulation of mitochondrial dynamics can reduce the severity of organ damage.

The integration of data on lactate, mtDNA, cytochrome c, and markers of oxidative stress forms the basis for a comprehensive assessment of a patient's mitochondrial status in intensive care. The biomarkers presented in Table 1 reflect different levels of damage, from metabolic adaptation to structural destruction of mitochondria, which opens up prospects for their use not only in diagnosis and prognosis, but also in monitoring the effectiveness of therapeutic interventions.

Table 1: Current biomarkers of mitochondrial damage in intensive care

Biomarker	Biological basis	Clinical significance	Prospects of application in ICU
Lactate	A product of glycolysis; reflects the metabolic restructuring of the cell	Marker of sepsis severity, shock, prognostic mortality rate	Dynamic monitoring of resuscitation efficiency
Lactate/pyruvate ratio	Cytosol redox status indicator	Indirect assessment of mitochondrial dysfunction	Early stratification of the risk of multiple organ failure
Circulating mtDNA	Release in case of mitochondrial damage; DAMP signal	Association with SVR and PON; correlation with SOFA	An early prognostic marker in intensive care

MT-ND1, MT-CO3, MT-CYB genes	Components of the mitochondrial respiratory chain	Reflect structural damage to mitochondria	Molecular monitoring after cardiac surgery
Cytochrome c	Respiratory chain protein; released during apoptosis	Relationship with myocardial dysfunction and CHF severity	Assessment of the severity of mitochondrial damage
Reactive oxygen species (ROS)	Oxidative stress, damage to mtDNA and membranes	Involvement in the development of organ dysfunction	Monitoring the effectiveness of antioxidant therapy
Malonic dialdehyde, isoprostanes	Lipid peroxidation products	A marker of the severity of oxidative stress	Additional assessment of the severity of the critical condition

The formation of multifactorial panels, including lactate, lactate/pyruvate ratio, circulating mtDNA and cytochrome c levels, with subsequent integration of these indicators into predictive models complementing the existing severity scales, seems promising. Such an approach can improve the accuracy of early risk stratification and optimize the choice of intensive care.

Thus, the biomarkers presented in Table 1 reflect different levels of mitochondrial damage, from functional shifts in energy metabolism to structural destruction of the respiratory chain and activation of inflammatory DAMP signals (Xia et al., 2020). Their complex interpretation allows us to move from an isolated assessment of individual indicators to a systematic understanding of the mitochondrial status of a patient in critical condition (Niu et al., 2023).

In this context, it is logical to consider factors (Li et al., 2023) that can modify mitochondrial function in intensive care practice, which determines the need to analyze the effect of anesthetics and intensive care methods on the bioenergetic processes of the cell.

The effect of anesthetics and intensive care methods on mitochondrial function

In modern intensive care practice, the effect of anesthetics and intensive care methods on mitochondrial function is considered as an important component of the outcome of critical conditions (Lee et al., 2021). Propofol, widely used for sedation and general anesthesia, is able to inhibit the activity of respiratory chain complexes and reduce mitochondrial membrane potential, which is accompanied by a decrease in ATP synthesis and increased formation of reactive oxygen species (Li et al., 2023). A number of experimental and clinical studies have shown (Andrieux et al., 2021) that prolonged propofol infusion results in a metabolic shift with signs of energy deficiency (Zhang et al., 2024), which underlies the propofol-associated syndrome under discussion (Zhu et al., 2023).

Inhaled anesthetics such as isoflurane and sevoflurane also demonstrate the ability to modify mitochondrial dynamics, enhancing fragmentation processes and facilitating the opening of the transitional permeability pore. These effects are associated with the activation of DRP1-dependent fission mechanisms and an imbalance between mitochondrial fusion and fragmentation, which affects the bioenergetics of neurons and cardiomyocytes. Contributions by Zhang Y., Li X., Sun T. (Zhang et al., 2025) showed that the expression of genes associated with mitochondrial function changes in patients after cardiac surgery depending on the anesthetic used, which confirms the clinical significance of these molecular shifts.

Equally important is the effect of vasopressors used in septic and cardiogenic shock, since excessive adrenergic stimulation can increase mitochondrial stress and disrupt microcirculation, limiting oxygen delivery to cells. In the reconstruction of signaling networks in sepsis, Liu S., Liang Q. (Liu et al., 2025) of metabolic pathways, including suppression of oxidative phosphorylation and activation of proinflammatory cascades closely related to mitochondrial dysfunction.

Infusion therapy can also indirectly affect mitochondria through changes in acid-base state, osmolarity, and tissue perfusion; excessive crystalloid loading can increase tissue edema and worsen mitochondrial respiration under hypoxic conditions (Zhao et al., 2023). Mechanical ventilation, especially when using high respiratory volumes and pressures, is associated with the development of ventilation-induced lung damage, which is accompanied by oxidative stress and a decrease in the efficiency of mitochondrial respiration in alveolar cells. A systematic analysis by McClintock C.R., Mulholland N., Krasnodembskaya A.D. (McClintock et al., 2022) emphasizes that mitochondrial biomarkers in ARDS reflect the degree of energy deficiency and correlate with the severity of respiratory dysfunction. Taken together, these data indicate that anesthetics and intensive care methods are not neutral with respect to cellular bioenergetics, and their effect on mitochondria can determine both short-term and long-term clinical outcomes.

Given the potential mitochondrial vulnerability of patients with sepsis and multiple organ failure, the choice of anesthetic tactics should take into account not only hemodynamic stability, but also the possible effect of drugs on oxidative phosphorylation processes and mitochondrial dynamics.

Therapeutic strategies for the correction of mitochondrial dysfunction

Mitochondrial diseases form a clinically heterogeneous group of hereditary conditions based on a defect in the respiratory chain and a decrease in ATP synthesis. To date, thousands of mutations affecting both mitochondrial and nuclear DNA have been described, which determines the complexity of pathogenesis and the variability of the clinical picture (Harijith et al., 2022). Violations of the assembly and functioning of protein complexes of the inner mitochondrial membrane lead to energy deficiency, especially in tissues with high oxygen consumption. Clinically, this is manifested by damage to the nervous system, myocardium, and skeletal muscles, as well as a variety of nonspecific symptoms that require differential diagnosis (Duan et al., 2022).

In conditions of both primary and secondary mitochondrial disorders, the development of therapeutic strategies aimed at restoring cellular bioenergetics is of particular importance. One of the key directions is considered to be metabolic resuscitation (Xu et al., 2021), which involves early correction of hypoxia, acidosis, and substrate metabolism disorders in order to stabilize oxidative phosphorylation (Yao et al., 2023). Maintaining adequate perfusion and oxygen delivery in anesthesiology and intensive care is considered not only as a hemodynamic task, but also as a way to prevent mitochondrial collapse (Guérin et al., 2016).

Antioxidant therapy is aimed at limiting lipid (Bellani et al., 2016) peroxidation and reducing the damaging effects of reactive oxygen species on membranes and mtDNA (O'Neill et al., 2023). The use of coenzyme Q10, succinic acid derivatives, B vitamins and other antioxidants helps to stabilize electron transport and reduce the severity of oxidative stress. A number of observations have shown that such therapy is accompanied by a decrease in lactate levels and improved exercise tolerance in patients with mitochondrial insufficiency (Mills et al., 2016).

Substrate support occupies a separate place and includes the appointment of L-carnitine, creatine, and Krebs cycle cofactors that provide fatty acid transport and optimize energy metabolism (Chen et al., 2024). These drugs do not so much replace defective links in the respiratory chain as create conditions for more efficient use of available metabolic pathways. In clinical practice, their use is justified both in congenital forms of deficiency and in secondary energy disorders accompanying critical conditions (Ren et al., 2021).

Mitoprotective drugs are considered as agents capable of stabilizing the membrane potential, preventing the opening of the transitional pore and reducing apoptotic activation. Such strategies include the use of cytochrome C, antihypoxants, and agents that affect mitochondrial dynamics. Their effect is to maintain the structural integrity of organelles and preserve the coupling of oxidation and phosphorylation processes (Xu et al., 2021).

The systematization of the main directions of metabolic correction used in clinical practice (Hernández-Cuervo et al., 2022) is presented in Table 2, which summarizes the groups of drugs, their mechanisms of action and the intended points of application in the respiratory chain.

Table 2: Therapeutic strategies for the correction of mitochondrial dysfunction

Therapeutic strategy	The main mechanism of action	Examples of funds	Clinical significance in anesthesiology and intensive care	Therapeutic strategy
Metabolic resuscitation	Optimization of oxygen delivery, correction of acidosis, maintenance of perfusion and conjugation of oxidation/phosphorylation	Hemodynamic control, infusion therapy, normalization of Hb and spo	Prevention of energy collapse in sepsis, shock, and postoperative complications	Metabolic resuscitation
Antioxidant therapy	Reduction of lipid peroxidation and mtDNA damage by reactive oxygen species	Coenzyme Q10, B vitamins, succinic acid derivatives, cytochrome C	Limitation of oxidative stress, stabilization of mitochondrial membranes	Antioxidant therapy
Substrate support	Provision of mitochondria with energy substrates and cofactors of the Krebs cycle	L-carnitine, creatine, B vitamins	Increased ATP synthesis, improved tolerance to hypoxia and stress	Substrate support
Mitoprotective therapy	Stabilization of membrane potential, prevention of mPTP opening, reduction of apoptosis	Cytochrome C, antihypoxants, membrane stabilizing agents	Preservation of the structural integrity of mitochondria in critical conditions	Mitoprotective therapy
Personalized therapy	Individual choice of metabolic support, taking into account genetic and clinical characteristics	Genetic testing, lactate and biomarker monitoring	Optimization of anesthetic tactics and intensive care	Personalized therapy

It should be emphasized that most mitoprotective strategies do not yet have a convincing evidence base at the level of large randomized clinical trials. Their use in intensive care requires further assessment of safety, dose-dependent effects, and impact on clinical outcomes. Therefore, Table 2 reflects the complex nature of therapy and demonstrates that effective correction of mitochondrial dysfunction requires a combination of antioxidant, substrate, and mitoprotective approaches.

Personalized therapy based on consideration of a genetic defect, severity of energy deficiency and clinical course features remains a promising direction (Sun et al., 2022). In anesthesiology, this involves an individual choice of anesthetics and infusion therapy regimens to minimize mitochondrial stress (Park et al., 2019). In intensive care, personalization includes

monitoring of lactate, oxygen transport parameters (Tong et al., 2021), and biomarkers of mitochondrial damage, followed by adjustments to metabolic support (Chen et al., 2018).
Thus, modern therapeutic strategies for mitochondrial dysfunction combine metabolic resuscitation, antioxidant protection, substrate support, and mitoprotection. Their complex and individualized use allows not only to reduce the severity of clinical manifestations, but also to increase the adaptive potential of the cell under stress and critical conditions.

Limitations of modern research
Despite the active development of this area, the existing data are characterized by significant heterogeneity of populations, differences in methods for determining mitochondrial biomarkers, and the lack of unified thresholds. In addition, the extrapolation of experimental models to clinical practice remains limited. This highlights the need for standardization of methods and prospective clinical trials.

CONCLUSION
Mitochondrial dysfunction in sepsis and ARDS is not a secondary phenomenon, but an independent mechanism that determines the depth of multiple organ failure and the clinical outcome. The identified mitochondrial-associated biomarkers, including ARID4B, RGS2, and TGM2, demonstrate diagnostic and prognostic significance and require further clinical validation in prospective studies. Modern methods of molecular analysis and machine learning expand the possibilities of early diagnosis and allow us to approach a personalized assessment of the patient's mitochondrial status. Complex therapy combining metabolic resuscitation, antioxidant protection and mitoprotective approaches is considered as a promising direction in anesthesiology and intensive care. Further clinical studies are needed to standardize biomarker-oriented protocols and assess their impact on the survival and functional outcome of critically ill patients. Thus, the transition from the macrohemodynamic paradigm to the molecular-metabolic interpretation of critical conditions opens up new opportunities for early diagnosis, personalization of therapy and improvement of patient outcomes in intensive care units.

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The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

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